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Investigating factors that affect survival of horses following treatment for synovial sepsis

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Abstract

Synovial sepsis is a major cause of death and loss of function in horses. Despite appropriate treatment there are cases that have persistent infections posing a welfare issue to horses. This thesis presents research identifying factors associated with outcomes.

Chapter one presents an introduction to the main principles of pathophysiology, diagnosis and treatment of synovial sepsis. Chapter two presents the first structured literature review on factors affecting outcomes after synovial sepsis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping review technique was used and through transparent and rigorous methodology it identified 61 studies investigating outcomes after synovial sepsis, with only eight using suitable methodology to investigate synovial sepsis outcomes. Data was charted and categorised to identify themes of research conduct and present the risk factors that have been previously found. Key features of the research conduct of previous studies included the small case numbers, lack of advanced statistical methods, marked variation in the inclusion criteria of cases, and different measurements of outcome.

Chapter three presents a multicentre study investigating synovial sepsis where 240 horses, presented for treatment during a 15-month period at ten hospitals. Data was recorded from admission, to a minimum of 365 days after surgery. Data capture forms were used to prospectively collect information on cases including signalment, injury details, surgical details and post-operative care. Descriptive data and univariable and multivariable cox proportional hazards models were used to investigate factors associated with poor outcomes. The long-term survival rate was 89.4% and factors identified as significantly associated with death included the limb affected (forelimb), increasing duration of surgery, increasing weight, the type of synovial structure affected (tendon sheaths and bursas), and increasing duration of antimicrobial therapy.

In conclusion, the research presented in this thesis provide important information to aid identification and indication of cases associated with worse outcomes. The results will provide invaluable evidence for vets and owners to improve welfare and outcomes for horses suffering from synovial sepsis.

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CHAPTER ONE

Introduction

Introduction

Synovial sepsis is one of the most common conditions causing emergency presentation of horses at referral hospitals (A Viljoena, 2009). It is a serious condition that can result in mortality or loss of use of the horse if not treated promptly and aggressively with large volume lavage and antimicrobial therapy. Survival and return to athletic function are key measurements of a successful outcome following surgical treatment. The current success rates for survival and return to athletic function are generally good, however, there are still cases which, despite gold standard care, fail to respond to treatment resulting in persistent infections and ongoing lameness (Crosby et al., 2019, Isgren et al., 2020, Post et al., 2003, Smith et al., 2006, Wright et al., 2003). There are only a small number of studies that investigate specific risk factors associated with failure to survive (Crosby et al., 2019, Findley et al., 2014, Milner et al., 2014,) and return to athletic function (Crosby et al., 2019, Isgren et al., 2020), and these studies often lack consistency and the results are difficult to compare. Further investigation of these risk factors is important to improve treatment outcomes and give important prognostic information to veterinarians and owners. This thesis will start with an introduction to synovial sepsis, and how it is diagnosed and treated.

Terminology

Synovial sepsis is the inoculation of the synovial membrane or synovial fluid with bacteria or other organisms that incite an inflammatory reaction that allows the establishment of viable microorganisms (Frisbie, 2012). The term synovial sepsis is used commonly in clinical practice to explain a number of different conditions, however, by definition, synovial sepsis describes cases where a bacterial infection within the synovial compartment has been confirmed with a positive bacterial culture, and the term synovial contamination is used otherwise (Frisbie, 2012). Bacterial culture from synovial samples can be unrewarding with variable success in producing a positive culture with a reported rate of 32-86% (Cousty et al., 2017, Gilbertie et al., 2018, Hepworth-Warren et al., 2015, Kidd et al., 2007, Robinson et al., 2016, Rodrigo et al., 2017, Schneider et al., 1992b, Taylor et al., 2010). In addition, with cultured samples taking up to 48 hours to yield a result, the practicalities of awaiting these results before starting treatment is not feasible. Therefore, in a clinical setting, the terms are often used interchangeably to describe conditions treated identically with large volume lavage and antimicrobial therapy. The term synovial sepsis is used to describe both terms throughout this thesis.

Pathophysiology of synovial sepsis

The main synovial compartments in the horse are joints, bursae or tendon sheaths, which all have a synovial membrane enabling these structures to have specific characteristics. A synovial joint is a fluid filled active cavity that produces and maintains a specific cellular, physical and chemical environment (Frisbie, 2012, Wright, 2002). Tendon sheath and bursae are fluid filled synovial sacs and are designed to reduced friction between adjacent moving structures. The pathophysiology of contamination and infection are similar for any type of synovial structure and the anatomy of the joint has been chosen to demonstrate the course of infection.

Inoculation

In mature horses, inoculation of a synovial cavity can be caused in several different ways including a penetrating injury or a wound, iatrogenically, via haematogenous spread, via local

spread, or by idiopathic means (Ashton, 2018, Byrne et al. 2020, Frisbie, 2012). The most common cause of infection is from penetrating traumatic injuries (McIlwraith et al., 2015, Milner et al., 2014, Wright et al., 2003). Signalment does not appear to influence prevalence of synovial sepsis. However, synovial structures on the distal limbs are more commonly affected than the upper limb most likely due to the location and frequency of wounds to these areas (Schneider et al., 1992b). Synovial infections following iatrogenic intervention can occur but are relatively rare (Borg and Carmalt, 2013, Brunsting et al., 2018, Hawthorn et al., 2016, Lapointe et al., 1992, Olds et al., 2006, Stöckle et al., 2018). Following elective arthroscopy the reported infection rate is between 0.5% - 1%, with factors increasing the risk of synovial sepsis including development of a surgical site infection, removal of a large osteochondral fragment (greater than 40mm) and arthroscopy of the femoropatellar joint compared to others (Brunsting et al., 2018). Similarly, following intra-synovial injections the risk is reported as low (0.04%) (Smith et al., 2019).

Synovial infections in foals differ from those in adult horses. Haematogenous spread due to transient or persistent bacteraemia is the most common pathophysiological cause. This can be due to immaturity of the neonatal animal or in combination with partial or complete failure of passive transfer of immunoglobulins (Annear et al., 2011). Microorganisms can enter the body from several routes including the umbilicus of normal foals, infected umbilical elements, the gastrointestinal tract or respiratory tract leading to a bacteraemia or septicaemia (Bohanon, 2005). The synovial membrane is a unique focus for infection due to the anatomy of the vasculature of the synovial membrane, where end loops of capillaries allow pooling of blood and the subsequent lodging of bacteria to facilitate inoculation of the synovial structure (Bohanon, 2005).

Within the literature, there is separation of self-sealing punctures caused by Blackthorn Prunus spinosus penetration from other causes of synovial sepsis. Blackthorn injury is a common cause of injury in horses jumping over hedges and results in an intense inflammatory reaction (Ashton, 2018). There is typically no bacterial growth associated with Blackthorn injury. Clinical signs are hypothesised to be due to a profound immune and

inflammatory response to plant proteins rather than a bacterial infection. For this reason, the disease is often classified as a synovitis (Ashton, 2018). In a recent case series on blackthorn injury, the authors also suggested that there could be microbial contamination due to the enterobacterium Pantoea agglomerans which is ubiquitously present and commonly isolated from plant material, but is difficult to isolate with standard techniques (Ashton, 2018). Within the human literature, there are a number of case reports which describe bacterial or fungal infections of synovial structures associated with thorn penetrations suggestive that as well as synovitis there is the ability for microorganism inoculation (Kim et al., 2022). With any foreign body penetration, or self-sealing puncture into a synovial structure, there is the possibility of taking external pathogens in (McIlwraith et al., 2015). This has resulted in significant cross-over with the clinical signs and treatment approach to these cases. Blackthorn injuries will be included within this discussion of synovial sepsis as they have done in previous investigations of synovial sepsis and synovial contamination (Wright et al., 2003).

Inflammatory cascade

After pathogens are introduced to the synovial structure, the normal synovial environment can fend off small numbers of pathogens using innate immunity such as the phagocytic activity of type A synoviocytes, as well as the production of cytokines and inflammatory mediators. For bacteria to colonise, they must overcome these defences as well as bind to tissue and establish growth (van Weeren, 2016). Bacterial colonisation within the joint triggers an acute inflammatory cascade as bacteria bind to pattern recognition receptors (PRRs) on synoviocytes (Frisbie, 2012).

Initial changes in the synovial membrane include hyperaemia and increased vascular permeability which allow inflammatory cells such as neutrophils and macrophages, as well as inflammatory mediators and complement factors to enter the joint from the blood (van Weeren, 2016). Neutrophils are the main inflammatory cell recruited to the joint which can directly kill intracellular bacteria via phagocytosis as well as indirectly by releasing destructive enzymes such as lysozymes, collagenase, gelatinase, cathepsin G and elastase (Spiers et al., 1994, van Weeren, 2016). Neutrophils and macrophages release free radicals that can degrade proteoglycans, collagen and hyaluronic acid, changing the composition of the

extracellular matrix and viscosity of the synovial fluid (van Weeren, 2016). A large release of inflammatory mediators, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFa) leads to a number of cascade reactions, including the increased production of certain matrix metalloproteinases (MMPs), which are zinc-dependent enzymes, from synoviocytes, chondrocytes and other inflammatory cells (Kidd et al., 2007). There are collagenases (MMPs 1, 8, 13), stromelysins (MMPs 3, 7, 10), gelatinases (MMPs 2, 9) and membrane type MMPs (MT-MMPs) which are all capable of degradation of the articular cartilage extracellular matrix (Kidd et al., 2007, van Weeren, 2016). A key component of the extracellular matrix is aggrecan which is a large proteoglycan molecule which has important characteristics that facilitate the articular cartilage to withstand compressive loads through the interaction of aggrecan with collagen fibrils (Roughley and Mort, 2014). In inflammatory states, such as after synovial sepsis, MMPs and specific degradative enzymes known as “a disintegrin and metalloproteinase with thrombospondin motifs” (ADAMTS) or “aggrecanases” degrade aggrecan and thereby reduce the joints normal ability to react to compressive loads. In addition, inflammatory cytokines such as IL-1 and TNFa decrease the synthesis of aggrecan leading to a severe impairment of the articular cartilage to function normally and alter the biomechanics varying the tolerance for loading and compressive forces further damaging the joint (Frisbie, 2012, Roughley and Mort, 2014, van Weeren, 2016). As the inflammatory cascade continues fibrin is produced as well as fibrinocellular conglomerate which is known as pannus. Pannus can physically alter the flow of synovial fluid within the joint, and can act as refugia for bacteria (van Weeren, 2016). The role of pannus in perpetuating further cartilage damage, acting as a source of inflammatory cytokines and proteinases, has been investigated extensively in human medicine (Cajas et al., 2019). These changes within the synovial structure significantly alter the homeostasis of the joint and push it towards a pro-inflammatory state. This causes alterations in cellular function and activity and results in reduced hyaluronic acid production, decreased proteoglycan concentrations in the extracellular matrix of cartilage, and increased collagen network damage (Hardy et al., 1998). An outcome is a biomechanically weak cartilage structure more prone to further perpetuating damage (Hardy et al., 1998). If these cases are not identified and treated quickly, then these changes can lead to osteoarthritis. The pathophysiological changes in

tendon sheaths or bursae are similar without the obvious changes to the articular cartilage which is lacking in these structures. The pathophysiological changes leads to chronic changes to the synovial membrane, alterations to the synovial fluid environment, development of adhesions, chronic lameness and similar loss of function of the synovial structure (Lugo and Gaughan, 2006, Mc Nally et al., 2013). In advanced stages, necrosis of the sheath and tendons can occur.

Presentation and diagnosis of synovial sepsis

Effective treatment of synovial sepsis starts with rapid and accurate identification of cases. Frustratingly, diagnosis can sometimes be challenging, and unless direct communication or the presence of foreign material within the synovial structure can be confirmed, there appears to be no single diagnostic test or clinical parameter that confirms this diagnosis. This poses an issue for clinicians and owners, as horses with synovial sepsis need aggressive and targeted treatment. If horses are incorrectly diagnosed, then it can lead to welfare issues as well as significant financial implications.

Clinical signs of synovial sepsis can depend on the duration and cause of the injury (Schneider et al., 1992b). The suspicion of synovial sepsis is increased with the presence of synovial effusion, heat, swelling and lameness. If a wound is present, exploration and palpation can sometimes identify direct communication with a synovial structure (Figure 1).

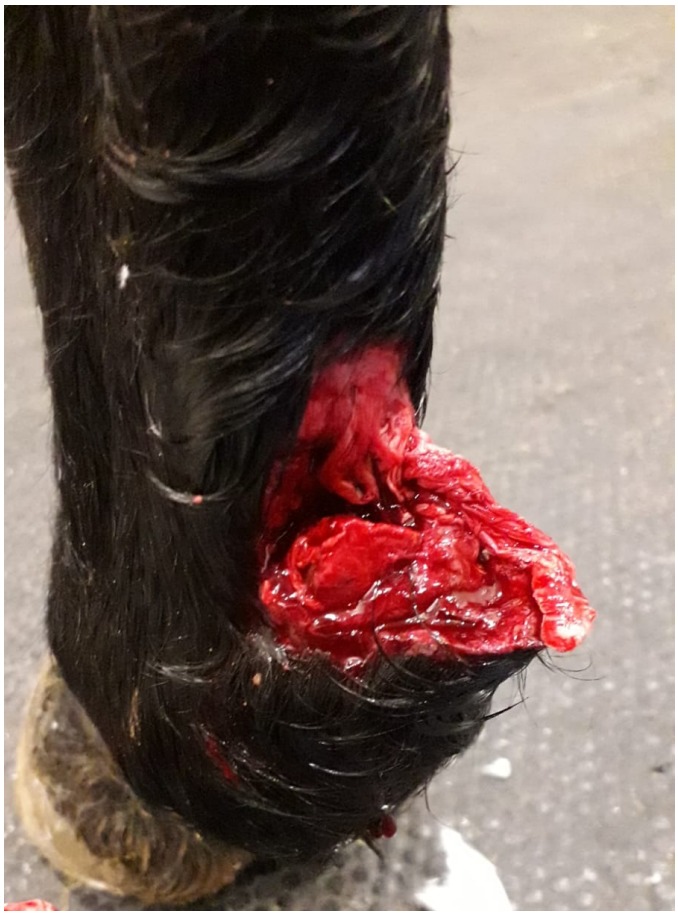

Figure 1: *Horizontal laceration to the palmar aspect of the left distal forelimb with obvious deep tissue involvement. The superficial and deep digital flexor tendons were found to be severed and the digital flexor tendon sheath was open*

Synoviocentesis is commonly used in a practical setting to aid diagnosis. Synovial fluid is sampled in a sterile manner and complete analysis includes a description of the gross appearance, assessment of the total nucleated cell count (TNCC) and differentials of types of white blood cell, total protein concentration (TP) and a cytological examination (Steel, 2008). At the time of sampling, assessment of the colour, opacity, volume, and viscosity can supplement the clinical suspicion of infection, however the gross appearance of synovial fluid can be influenced by other non-infectious pathology and is not specific (Frisbie, 2012, Richardson and Ahern, 2012). Figure 2 shows the appearance of a grossly affected synovial sample suggestive of synovial sepsis.

Figure 2*: A grossly discoloured and purulent synovial sample suggestive of synovial sepsis*

The normal synovial environment has a low cell population with the nucleated cell count within equine synovial joints between 0.2-1.0 x10^9 cells/L and between 0.2-3.5 x10^9 cells/L for tendon sheaths (Steel, 2008). The normal distribution of cells within this scant population includes neutrophils, lymphocytes and macrophages, with neutrophils contributing approximately 10% (Richardson and Ahern, 2012). Any abnormal substance entering a synovial structure causes an increase in the total nucleated cellular population, however bacteria inoculation creates the greatest increase in this value (Richardson and Ahern, 2012, Tulamo et al., 1989a). Different studies recommend different synovial parameters as an indication for synovial sepsis with TNCC values ranging between 5-30 x 10^9 cells/L (Crosby et al., 2019, Milner et al., 2014, Wright et al., 2003). The upper value of this range (30 x 10^9 cells/L) appears to be based on an experimental study where Staphylococcus aureus was injected into the tarsocrural joints of healthy horses and sequential synovial fluid analysis was performed which showed that 8-12 hours after inoculation the TNCC was between 22.9-37.1 x 10^9 cells/L, with 80% of horses being >50 x 10^9 cells/L when clinical signs started to become apparent (Tulamo et al., 1989b). In a practical setting, the TNCC can vary significantly and synovial pathology other than infection can cause marked elevations in the TNCC such as

non-infectious synovitis seen with degenerative joint disease, making the TNCC a less reliable marker. This was demonstrated by another experimental study where a sterile synovitis, mimicking a clinical acute traumatic synovitis, was induced into horses with injection of lipopolysaccharide at low doses which resulted in TNCC values of 31 x 10^9 cells/L (Palmer and Bertone, 1994). Similarly, in human healthcare, a TNCC of 50 x 10^9 cells/L increases the suspicion of synovial sepsis, however, other pathological conditions such as gout (an inflammatory arthritis caused by uric acid but not associated with infection) can cause similar rises in TNCC (Turner et al., 2021). Further to this, within an infected synovial structure, the TNCC can also vary depending on the duration of the injury to time of synoviocentesis (Tulamo et al., 1989b), the number of times sampling has occurred (Jacobsen et al., 2006), whether intra-articular corticosteroids were the cause of the infection (Steel, 2008, Tulamo et al., 1989a), which bacteria have caused the infection (Steel, 2008), the presence of an open draining wound (Frees et al., 2002, Milner et al., 2014), or the presence of fibrin (Richardson and Ahern, 2012). Madison *et al.* found TNCC values less than 10 x 10^9 cells/L in culture positive joints which highlights that TNCC is not always a reliable indicator of sepsis and suggests that adhering to such strict "cut-off" counts can lead to inappropriate diagnosis (Madison et al., 1991). Another consideration is the presence of an open synovial cavity. If a wound communicating with a synovial structure is present, the inflammatory mediators can leak from the structure and therefore lead to a false or misleadingly low TNCC. These examples highlight the limitations of using TNCC for the diagnosis of synovial sepsis.

Synovial total protein concentration also lacks specificity and sensitivity for infection over other synovial pathology and varies with similar factors to TNCC. Total protein concentrations within equine synovial structures are normally less than 20g/L (Steel, 2008). It has been suggested that the total protein concentration may more accurately represent the degree of inflammation in the joint as it represents the inflammatory mediators being released by the synoviocytes and also represents the degree of vascular permeability which may explain why a higher total protein concentration both pre and post-operatively has been shown to be an indicator of poor survival (Cousty et al., 2017, Milner et al., 2014).

Because neither TNCC nor TP have proved to be pathognomonic of synovial sepsis diagnosis there has been increasing interest to identify a specific and sensitive biomarker to differentiate infection with other synovial pathology as early as possible within the disease process. Serum amyloid A (SAA) is the major acute phase inflammatory protein in the horse and is present in small amounts in normal equine synovial structures (Jacobsen et al., 2006, Ludwig et al., 2016). SAA is normally produced by the liver in response to inflammation and infection, however it can also be produced by synoviocytes in response to localised inflammation and infection within the joint (Jacobsen et al., 2006). Elevation of SAA in both serum and synovial samples have been demonstrated in response to synovial infection with good sensitivity and specificity when compared to non-septic causes of synovial inflammation in an experimental and clinical setting (Ludwig et al., 2016, Robinson et al., 2017). Further to this, serial synovial SAA measurements may also prove useful in therapeutic monitoring post-operatively as it has been shown to not be affected by repeat synoviocentesis compared to TP and TNCC (Jacobsen et al., 2006). However, more research is required to establish an SAA concentration that indicates synovial sepsis with high sensitivity and specificity and to evaluate the influence of the timing of sampling.

Measurement of synovial biomarkers such as matrix metalloproteinases (MMPs) and lysosome and myeloperoxidase enzymes has gained interest. In a normal joint, MMPs activity is tightly regulated through presence of tissue inhibitors of metalloproteinases (TIMPs). However, in inflammation, due to the increase in MMP concentration, this balance is disrupted, and increased MMP activity leads to degradation of the extracellular matrix and articular cartilage (Kidd et al., 2007). MMP-2 and MMP- 9 have been shown to be useful in the diagnosis of synovial sepsis, with increased levels of their pro-enzymes in both inflamed and septic joints. Elevated levels of pro-enzyme MMP-9 have specifically been found in septic joints rather than inflamed and may prove a more specific marker of synovial sepsis (Abdelhaleem et al., 2021, Kidd et al., 2007). In addition, the ratio of pro-enzymes of MMP-9: MMP-2 was predictive of survival following treatment and may provide more prognostic information (Abdelhaleem et al., 2021, Kidd et al., 2007). In a recent experimental study, increased activity of synovial enzymes myeloperoxidase and lysozyme was found to be

sensitive and specific and allowed a rapid diagnosis of synovial sepsis (Haralambus et al., 2022). In humans, measurement of the degradation products of the extracellular matrix proteoglycan aggrecan are used as a biomarker for disease status (Swearingen et al., 2010). However, measurement of MMPs, lysozymes myeloperoxidase enzymes and aggrecan degradation products are not widely available unless sent to specialist laboratories limiting the usefulness in a clinical setting as a rapid adjunctive test at this stage. Other synovial fluid markers that have been investigated but have limited use as accessory tools for the diagnosis of synovial sepsis include pH, lactate, glucose and interleukin receptor antagonist. These biomarkers either have poor sensitivity and specificity for differentiating septic and non-septic structures or are not widely available (Steel, 2008).

Microbiological culture is considered the gold standard technique for the confirmation of synovial sepsis, and when combined with in-vitro sensitivity testing, it can provide essential information with regard to targeted antimicrobial therapy (Richardson and Ahern, 2012). The main disadvantage of bacterial culture as a diagnostic tool is the significant time delay of 24-48 hours for results which render it unhelpful for immediate confirmation of synovial sepsis in a clinical setting. Most clinicians would not delay treatment until the culture results, and so although this is the gold standard technique for diagnosis, most clinical decisions pre-operatively are based on other factors. In addition, there is variable success in producing a positive culture with a reported rate of 32-86% (Cousty et al., 2017, Gilbertie et al., 2018, Hepworth-Warren et al., 2015, Robinson et al., 2016, Rodrigo et al., 2017, Schneider et al., 1992b, Taylor et al., 2010). The success of a positive culture is dependent on several factors including the virulence and numbers of the pathogens, the method of culture, and the bactericidal properties of the synovial fluid (Richardson and Ahern, 2012). The most frequently cultured bacteria from infected synovial structures include Staphylococcus aureus (Taylor et al., 2010), Enterobacteriacaea (Schneider et al., 1992b) and Streptococcus equi (Rodrigo et al., 2017). Where bacterial culture is more practically useful in is guiding antimicrobial therapy post operatively and also giving prognostic information. Positive culture results can influence prognosis and it has been shown that when certain pathogens have been cultured it can be a negative prognostic indicator for survival and return to athletic

function compared to a negative culture (Gilbertie et al., 2018, Taylor et al., 2010). Further to this, if a multi-drug resistant (MDR) organism is identified, it is also associated with reduced survival to discharge (Gilbertie et al., 2018). To improve the chance of a positive culture, synovial samples should be combined with a blood culture medium. A recent study found that synovial samples in a blood culture vial were 1.7 times more likely to yield a positive culture compared to samples submitted in a serum tube (Pearson et al., 2023). In addition, it is recommended that synovial samples are collected prior to the administration of antimicrobial treatment (Frisbie, 2012). There are only limited recommendations within the literature on the minimum volume of synovial fluid or blood culture medium volume to improve culture results for equine synovial samples, and future research in this area would be beneficial.

Cytological examination of synovial fluid is an important component of diagnosis. A smear of synovial fluid collected from an Ethylenediaminetetraacetic acid (EDTA) sample can be air-dried and then stained with an appropriate stain. The slide can then be analysed with a microscope. Key subjective and objective features of the cellularity are observed including an assessment of the number of cells and the type of cells present and the presence of both intra and extra-cellular micro-organisms. Normal synovial fluid has a low cellularity and is populated with mononuclear cells. The presence of greater than 90% degenerative neutrophils with the presence of intracellular bacteria has been suggested to be definitive for a cytological diagnosis of synovial sepsis (Steel et al., 2008).

Molecular methods of isolating and identifying bacteria are gaining interest in human and veterinary cases. The use of the broad range ribosomal RNA (rRNA) gene polymerase chain reaction (PCR) had a very high sensitivity (91.8%) and specificity (>90%) for detecting bacterial DNA when synovial samples were first incubated in blood culture medium (Pille et al., 2004, Pille et al., 2007). However, no antimicrobial sensitivity information is available with this testing process which may limit its clinical use in the future. In addition, a recent human study has found that measuring bacterial DNA using PCR techniques in the synovial fluid of infected structures did not improve the diagnosis of synovial sepsis compared to traditional culture and direct cytological examination (Coiffier et al., 2019).

Although synovial fluid analysis is often an essential part of the diagnostic work-up, the literature so far highlights a lack of clarity about which parameters to use and how different clinical presentations and time courses affect the key values measured. In addition, when comparing the results of studies, it is apparent that research groups use different values for the diagnosis of synovial sepsis which means comparison between groups is challenging. Within human health care, there are similar issues in diagnosis. A systematic review investigating the diagnosis of septic arthritis in people found that “no investigation is more reliable in the diagnosis of septic arthritis than the opinion of an experienced doctor” highlighting the importance of considering the clinical presentation in its entirety, although not removing subjectivity from the decision (Mathews et al., 2007).

Ultrasonographic and radiographic examination are the most commonly used diagnostic imaging techniques in the work-up of cases suspected of synovial sepsis, and diagnostic imaging findings can increase the suspicion of synovial sepsis or contamination. Key features that can be assessed include but are not limited to, the articular cartilage, the presence of osseous pathology, the presence of soft tissue pathology, the echogenicity of the synovial fluid, the thickness and appearance of the synovial membrane, and the presence of foreign material (Beccati et al., 2015). It has been shown that the most important clinical parameter affecting ultrasonographic appearance of synovial sepsis cases was the time between injury and examination, and ultrasound findings of fibrinous loculations, synovial effusions and synovial membrane thickening being the most commonly identified in cases of synovial sepsis (Beccati et al., 2015). However, if a penetrating wound was the cause of the injury, the presence of gas subcutaneously could prevent accurate ultrasonographic assessment (Beccati et al., 2015). Plain radiography is commonly used in the initial work up and is useful in assessing the presence and severity of any bone damage associated with synovial sepsis cases. This must be quantified before treatment is started firstly in regards to anaesthesia risks and secondly as bone pathology has been shown to be a negative outcome predictor in cases of synovial sepsis (Kelmer et al., 2012, Isgren et al., 2020). Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003). Positive contrast radiography can also be used to

confirm communication of wounds or penetrating injuries with synovial structures. This technique has limited sensitivity (59.1%) but a high specificity (86.4%) and negative predictive value (80.9%) when these findings are present (Bryant et al., 2019). Advanced imaging, including magnetic resonance imaging (MRI), computed tomography (CT) and nuclear scintigraphy can be used to aid diagnosis. Low field magnetic resonance imaging (MRI) has been shown to provide information after nail penetration with regard to the number of penetrating tracts, degree of soft tissue damage and synovial involvement (Heer et al., 2015).

Treatment

The aims of treatment for synovial sepsis are the removal of any foreign material, contaminated or devitalised tissue, the elimination of microorganisms, the removal of inflammatory mediators and the restoration of a normal functioning synovial structure (McIlwraith et al., 2015). In a clinical setting, this relates to large volume lavage, surgical debridement, antimicrobial therapy and anti-inflammatories. These treatment techniques are often used in combination which makes evaluating the efficacy of any specific factor difficult when assessing the success of treatment.

Lavage and drainage

Lavage is an essential treatment component of synovial sepsis to eliminate any microorganisms and to remove any inflammatory cells and mediators from the synovial structure (Richardson and Ahern, 2012). Even after the elimination of the bacteria, the synovial mediators within an inflamed synovial structure can potentiate destructive changes and lavage allows removal of these. This highlights the importance of a dual approach of antimicrobials and lavage (Hardy et al., 1998). Techniques include through-and-through lavage, intra-synovial catheters, arthrotomy and endoscopy (Frisbie, 2012). Through-and-through lavage includes placing wide bore needles or catheters within the synovial structure to facilitate large volume lavage without direct visualisation of the synovial structure (Richardson and Ahern, 2012). It can be performed under standing sedation or general anaesthesia. Figure 3 demonstrates through-and through lavage in a standing horse. Endoscopy is a minimally invasive technique and has mostly replaced arthrotomy and through-and-through lavage as the gold standard technique for synovial sepsis (McIlwraith et al., 2015) however, both through-and-through lavage and arthrotomy are still acceptable and useful treatment techniques when finances preclude endoscopy. Case series describing outcomes after through-and-through lavage report between 73-93% survival to discharge rates (Duggan and Mair 2019, Meijer et al., 2000, Wereszka et al., 2007) which is comparable to endoscopic lavage. Endoscopic lavage offers numerous advantages, however, does require training and expensive equipment. In addition, knowledge of the anatomy and technique are important, and the surgeon must make every effort to lavage the entire synovial structure and any less accessible areas where microorganisms and inflammatory tissue could

be. In addition, they should look for any evidence of articular cartilage, soft tissue or osseous pathology. It is not infrequent that bone, cartilage or soft tissue pathology is not diagnosed pre-operatively. For example, in one study, only 49% of cases with endoscopic evidence of bone, cartilage or soft tissue pathology had these identified prior to surgery (Wright et al., 2003). Figure 4 shows a wound communicating with the digital flexor tendon sheath being lavaged under endoscopic guidance.

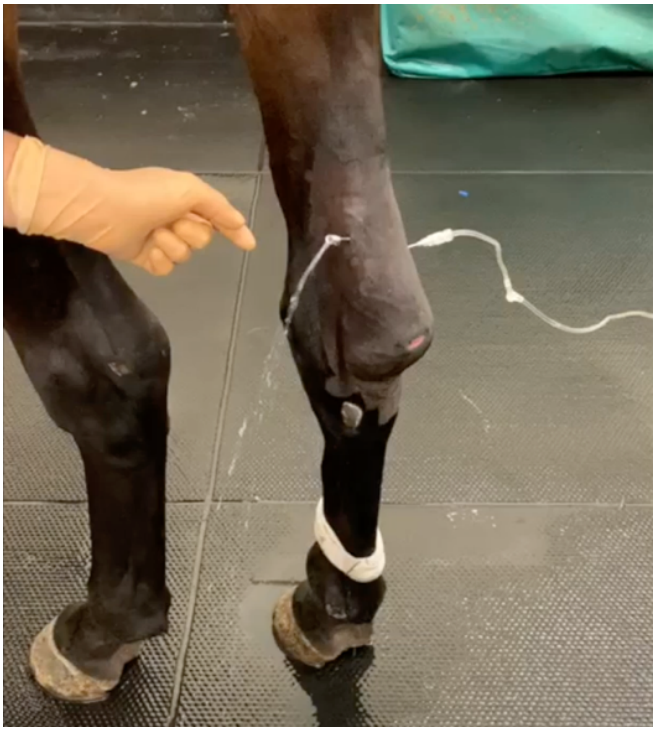

Figure 3: *Through and through lavage of an infected calcaneal bursa in a standing sedated horse.*

Lavage can also be combined with drainage to allow elimination of inflammatory mediators and bacteria out of the structure as well as improving horse comfort by reducing intra-synovial pressure (Schneider et al., 1992a). Examples of drainage include leaving the synovial structure portals or wound open, intra-synovial catheters, or active or passive drains (Richardson and Ahern, 2012). Disadvantages of using drainage include the open communication of the synovial structure with the environment which can allow ascending bacterial infection, the intensive monitoring with frequent sterile bandage changes increasing cost, as well as longer convalescence periods due to complications with wound healing (Schneider et al., 1992a). The commonly used treatment techniques are compared in Table 1. This highlights the number of advantages of endoscopic lavage, especially in regards to

direct visualisation of the pathology within the synovial structure. There are no studies describing outcomes of synovial sepsis without lavage identified in a recent scoping review on synovial sepsis treatments (de Souza et al., 2022).

Figure 4: *Endoscopy of the digital flexor tendon sheath for treatment of a septic synovial sheath associated with a wound.*

Debridement of any inflammatory tissue is important, especially in well-established cases of synovial sepsis. Areas of osseous abnormality associated with the initial cause of injury such as fragmentation or fractures should be debrided down to healthy tissue. In addition, any soft tissue pathology, such as tendinous lacerations should be well debrided to remove any contaminated tissue and promote adequate healing (McIlwraith et al., 2015). Synovectomy is the removal of the synovial membrane and this can be performed using a variety of methods including mechanical resection and laser ablation. It is often reserved for chronic cases or refractory cases, and its use as a first line treatment is controversial (McIlwraith et al., 2015). By removing the synovial membrane, this can directly remove any pannus associated with the

membrane, as well as directly removing any bacteria adhered to the membrane and reducing bacterial numbers (Doyle-Jones et al., 2002, Theoret et al., 1996). It is also hypothesised, that by removing parts of the synovial membrane, this can increase the penetration of systemically administered drugs (Doyle-Jones et al., 2002, Theoret et al., 1996). As referenced earlier, the synovial membrane has several important physiological roles and after resection, this alters the normal synovial environment. In addition, it can take up to four months for adequate healing of the membrane to occur, and when it has, it is structurally altered on a gross and histological level with an avillous appearance and increased fibrosis within the subintima layer (Theoret et al., 1996). This indicates that synovectomy should be performed with caution unless indicated.

Table 1: *Comparison of the different lavage techniques commonly used for the treatment of synovial sepsis in horses.*

Treatment technique	Advantages	Disadvantages	Survival Rate
Through-and-through lavage	Quick and technically easy to perform No specialist equipment or training needed Inexpensive	Only smaller volume of lavage fluid used (although recent experimental studies suggest 1 litre lavage fluid can remove microspheres from the tarsocrural joint – Loftin et al., 2016) No visualisation of the synovial structure to identify bone or soft tissue pathology No ability to remove large inflammatory tissue e.g. pannus Repeated lavage can be necessary (Meijer et al., 2000)	73-93.7% (Meijer et al., 2000, Wereszka et al., 2007, Duggan and Mair 2019)
Arthrotomy	Adequate visualisation Ability to remove fibrin and pannus Large volume lavage possible (Bertone et al., 1992) Can be combined with open drainage (leaving the arthrotomy incision open)	Complications associated with arthrotomy incision (delayed healing, synovial fistulae formation) (Bertone et al., 1987b) Ascending bacterial infection (Bertone et al., 1992) Expensive GA Drying of articular cartilage (Paterson. et al., 2016)	92% (Schneider et al., 1992a)
Endoscopic lavage	Excellent visualisation of the synovial cavity Able to identify and debride devitalized or irreparably damaged tissue Directed targeted lavage into synovial recesses that may be difficult flush	Specialist equipment needed Expertise and training to perform Expensive GA	70-90% (Wereszka et al., 2007, Wright et al., 2003)

	Able to remove inflammatory debris, blood and/or fibrin clots, pannus and adhesions Minimally invasive technique (reduced incisional complications and convalescence)	

(Abbreviations: GA- general anaesthesia, Survival rate – survival to discharge or to 1 year post-operatively)

Wounds are a common cause of synovial sepsis and treatment should be carefully planned alongside treating the synovial structure. During surgery, time should be taken to fully explore the wound and identify the location of synovial communication to allow for debridement of contaminated tissue, and assess any potential soft tissue or osseous damage associated with the wound. In addition, for chronic and severe wounds, the method of closure and potentially immobilisation should be considered carefully to optimise healing (Figure 5).

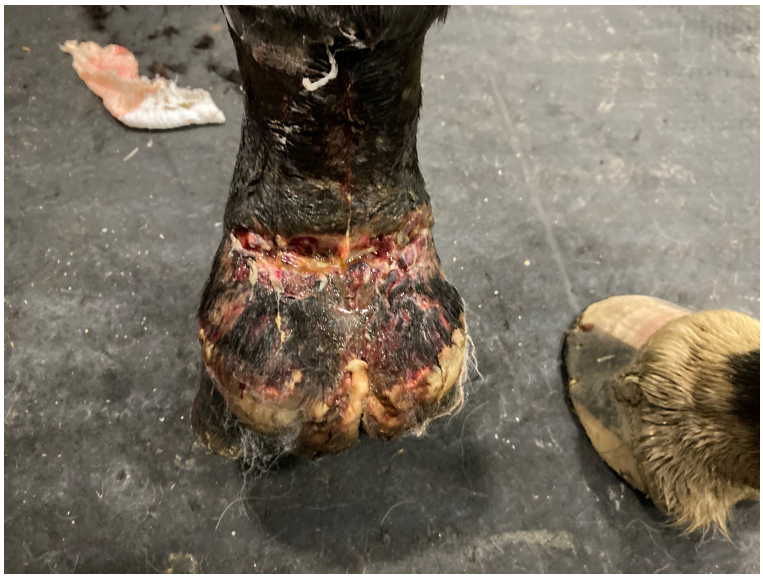

Figure 5: *Chronic severe full skin thickness wound affecting the palmar pastern of the left forelimb communicating with the palmarodistal pouch of the digital flexor tendon sheath.*

There have been no clinical studies investigating the volume of fluid required to lavage an equine synovial structure for successful treatment of synovial sepsis. An experimental study

comparing through and through needle lavage and arthroscopic lavage found that small volumes (one litre) of lavage fluid with needle lavage multiple portals was of greater benefit at removing microspheres from normal tarsocrural joints than arthroscopic lavage with higher volumes and only one egress portal (Loftin et al., 2016). Future studies investigating lavage volume in clinically abnormal joints would be useful to qualify this experimental research.

The ideal synovial lavage solution should be bactericidal and nontoxic to the synovial membrane and articular cartilage, however balanced electrolyte solutions that are commonly used do not possess any bactericidal effects (Wilson et al., 1994). Addition of an antiseptic to a balanced electrolyte solution could be a solution to this issue, however, their use as an additive to synovial fluid lavage is controversial. Chlorhexidine lavage at a concentration of 0.05% caused synovial ulceration, inflammation, and abundant fibrin accumulation in normal horse tarsocrural joints and is not recommended as an addition (Wilson et al., 1994). Furthermore, it has been shown in human studies that chlorhexidine may have more deleterious effects in osteoarthritic joints by impairing cartilage metabolism (Best et al., 2007). Povidone iodine has also been investigated as an additive to lavage solutions. The presence of protein within the synovial structure means longer exposure times or higher concentrations are needed for povidone iodine to work (Wichelhaus et al., 1998). However, an experimental study found that lavage of the digital flexor tendon sheath with 0.5% povidone iodine caused severe synovitis, whereas 0.1% povidone iodine did not (Baird et al., 1990). Another human antiseptic Polyhexamethylene biguanide (PHMB) has broad spectrum bactericidal activity and low cytotoxicity compared to the other described antiseptics but requires long periods of exposure up to 20 minutes at a standard concentration (0.04%) (Röhner et al., 2011). Furthermore, PHMB has been shown to promote apoptosis on primary human chondrocytes in vitro which may suggests further research is required before it is used in a clinical setting (Röhner et al., 2011).

In the literature, there are a limited number of studies comparing techniques with outcome, with most data being derived from retrospective case series (Wereszka et al., 2007) or outdated experimental studies (Bertone et al., 1992, Bertone et al., 1987b). Wereszka *et al*. compared lavage method on return to athletic function one year post-operatively and found

no significant effect on lavage technique (through-and-through, tenoscopy, open tenosynoviotomy) with outcome (Wereszka et al., 2007). However, in this study, there were only small numbers of horses in each treatment group. The distribution of technique was not randomly allocated and the through-and-through lavage technique utilised also included making instrument portals to remove fibrin and to debride adhesions gaining the advantages of the other techniques (Wereszka et al., 2007). This study illustrates the lack of good quality evidence available and the need for a large number of cases to be able to draw useful reliable conclusions.

Antimicrobials

Culture and sensitivity should dictate the choice of antimicrobials; however, this often takes up to 48-72 hours after collection, and broad spectrum antimicrobial therapy should be initiated as soon as a diagnosis of synovial sepsis is made or suspected. A combination of systemically and locally administered antimicrobials is normally used. There are limited studies investigating antimicrobial treatment without lavage. A study comparing antimicrobial treatment as a sole treatment compared to antimicrobial treatment and various lavage protocols in experimentally induced synovial sepsis showed that antimicrobial therapy alone was not effective at significantly reducing the TNCC and total protein in synovial fluid samples after 21 days (Bertone et al., 1987b).

Systemic

The most commonly used broad spectrum antimicrobial combination for synovial sepsis is penicillin (potassium, sodium, or procaine) and an aminoglycoside (gentamicin or amikacin) for gram-positive and gram-negative coverage respectively (Richardson and Ahern, 2012). It has been shown that most systemically administrated antimicrobials penetrate and are active in normal and infected synovial structures, however there is a time delay between maximum serum concentration and maximum synovial concentration (Morton, 2005). Furthermore, the synovial concentration may not be equivalent to the serum concentration, and may be below the minimum inhibitory concentration (MIC) during the inter-dosing interval (Cook et al., 1999, Lloyd et al., 1990). By increasing systemic dosage frequency and concentrations of antimicrobials this could lead to harmful side-effects. As a result, techniques for local

administration of antimicrobials have been developed to achieve high local concentrations with minimal adverse side-effects.

Local

There are many techniques for local administration of antimicrobials including intra-synovial injections, intra-venous regional limb perfusion, intraosseous regional limb perfusion, intra-synovial catheters, and antimicrobial impregnated biomaterials (Frisbie, 2012). Direct injection of antimicrobials into the synovial compartment leads to immediate synovial concentrations above MIC for most bacterial isolates dependent on the dose administered (Lescun et al., 2006, Lloyd et al., 1988, Lloyd et al., 1990). Intra-synovial injection of antimicrobials is performed after aseptic preparation of the structure and would need to be repeated daily or every other day to achieve adequate therapeutic goals. Possible disadvantages with intra-synovial administration include the need for multiple synoviocenteses that can cause localised synovitis, increased risk of ascending bacterial infection and added expense of frequent bandage changes (Richardson and Ahern, 2012). Amikacin, gentamicin, ceftiofur, imipenem, meropenem and vancoymycin have all been reported to be safely used in synovial structures (Lloyd et al., 1988, Lloyd et al., 1990, Richardson and Ahern, 2012). There is an increasing body of evidence that amikacin may not be as safe as once thought within the intra-synovial environment. For example, in vitro and in vivo studies in healthy joints have identified that amikacin used at normal dose rates (250-500mg/joint) induced rapid and pronounced direct dose-dependent chondrocyte death (Pezzanite et al., 2020). In addition, it has been found that amikacin can also lead to an increased production of chondrocyte degradation products and pro-inflammatory markers (Pezzanite et al., 2021). Further studies are required to establish this relationship and find ‘safe’ dosages to use within synovial structures. In addition, further investigation is needed to evaluate any differences in the pharmacokinetics of amikacin in infected synovial structures. Studies investigating the cytotoxic effects of other intra-articular drugs are limited, however, there is evidence to suggest that there are less destructive drugs to the articular environment such as ceftiofur, imipenem and gentamicin (Pezzanite et al. 2021). However, ceftiofur and imipenem are time dependent rather than concentration dependent antimicrobials and depending on the dose used may not reach and sustain appropriate MIC for common bacteria isolated for synovial

sepsis precluding to antimicrobial resistance. In regards to the treatment of synovial sepsis, it is obvious that local administration of antimicrobials offer advantages, however no studies look at the timing or frequency of local administration in clinical cases and the effect on short or long term outcomes.

Regional limb perfusion (RLP) of antimicrobials is another frequently used technique to deliver high concentrations of antimicrobials to the local area in sedated and anaesthetised horses (Butt et al., 2001, Rubio-Martinez and Cruz, 2006). Regional limb perfusion can be given via intravenous or intra-osseous routes and both involve using a tourniquet to isolate the affected limb to increase the concentrations of antimicrobials locally. Intravenous regional limb perfusion (IV-RLP) involves identifying a peripheral vessel that supplies the isolated region and using it to instil an antimicrobial infusion either as a bolus or a constant rate infusion (CRI). This creates a concentration gradient for the antimicrobial to diffuse from the vascular compartment into the extra-vascular space including synovial structures. In addition, a long-term indwelling catheter can be used to facilitate frequent IV-RLP administration however this has been reported with up to a 26% complication rate, including the development of phlebitis of the used vessel and cellulitis of the surrounding area (Kelmer et al., 2009, Kelmer et al., 2012). Synovial fluid antimicrobial concentrations after IV-RLP are not as high as those achieved after direct intra-synovial injection (Lloyd et al., 1990), however, they can reach significantly higher than the MIC achieved with systemic administration (Butt et al., 2001, Rubio-Martinez and Cruz, 2006). For these reasons, the best antimicrobials to use in IV-RLP are concentration dependent such as aminoglycosides like amikacin and gentamicin (Rubio-Martinez and Cruz, 2006). The usefulness of IV-RLP in synovial sepsis has been shown in experimental and clinical studies of synovial sepsis with minimal complications (Rubio-Martínez et al., 2012, Whithair et al., 1992). However, there is significant variation in doses, antimicrobials used, technique of administration, frequency of administration and the use of local anaesthetic as an adjunctive treatment (Biasutti et al., 2021). A recent meta-analysis investigating the influence of technique on the local concentration of antimicrobials achieved identified that wide rubber tourniquets and concurrent local analgesia offered significant advantages for achieving high antimicrobial

concentrations in IV-RLP (Redding et al., 2022). IV-RLP can also be used simultaneously with joint lavage with minimal loss of antimicrobial in the egress fluid (Alkabes et al., 2011). However, further research is needed to establish what benefit IV-RLP has in specific synovial sepsis cases. It has been shown to be negatively associated with return to athletic function in two retrospective case series (Pille et al., 2009, Wright et al., 2003), but this may be due to case selection bias as IV-RLP was not randomly allocated and horses with concurrent osteomyelitis or persistent infection received IV-RLP as an adjunctive treatment which could influence these results. Additionally, further studies are required to compare the cytotoxic effects of amikacin when used in IV-RLP and intra-articular medication.

Intra-osseous regional limb perfusion (IO-RLP) can also be used to deliver local antimicrobials. Using a similar technique to IV-RLP with the placement of a tourniquet, IO-RLP requires aseptic drilling of a small strategically placed unicortical hole into the medullary cavity and placing an intraosseous bone port through which antimicrobials can be administered (Butt et al., 2001, Rubio-Martinez et al., 2005, Scheuch et al., 2002). There have been several case controlled studies comparing IV-RLP techniques and IO-RLP in healthy tissues (Butt et al., 2001,Scheuch et al., 2002) with good concentrations of the antimicrobial achieved, however the is some evidence to suggest that depending on the location IV-RLP can produce higher concentrations than IO-RLP, especially in regards to the distal interphalangeal joint (Butt et al., 2001) and the tarsocrural joint (Scheuch et al., 2002). Further to this, toxic osteonecrosis secondary to IO-RLP and pathologic fracture has been reported potentially making IV-RLP a safer and more useful localised treatment technique (Parker et al., 2010).

Antimicrobial impregnated biomaterials can also be used to deliver local antimicrobial therapy and are broadly categorised into two categories: bioabsorbable and non-absorbable. Polymethyl methacrylate (PMMA) is a non-absorbable high-density plastic that when antimicrobials are added can reach up to 200 times the concentration achieved by systemic administration (Holcombe et al., 1997). Antimicrobial elution occurs in a bimodal pattern dependent on the antimicrobial used. It normally involves rapid elution in the first 24 hours

followed by slow release over the following months to years (Richardson and Ahern, 2012). The implants are non-absorbable and should be removed after 4-6 weeks as they can cause localised inflammation (Richardson and Ahern, 2012). However, they can be placed peri-articularly and aid in the treatment of acute and chronic synovial sepsis (Butson et al., 1996, Holcombe et al., 1997). Plaster of Paris (POP) is a bioabsorbable antimicrobial impregnated biomaterial and is degraded and absorbed by the body and therefore does not need to be removed like PMMA. Both PMMA and POP have been associated with increased risk of cartilage damage in synovial structures associated with the motion of the implant and therefore should be used judiciously (Richardson and Ahern, 2012). PMMA beads have been reportedly used with success as an adjunctive treatment for sepsis of the small tarsal joints, acting as a slow release antimicrobial where lavage is often difficult to achieve (Booth et al., 2001). Other absorbable implants such as collagen sponges are much less traumatic to cartilage and gentamicin soaked collagen sponges have been reported to have excellent success as an adjunctive to arthroscopic lavage in the treatment of synovial sepsis (Steiner et al., 2000, Summerhays, 2000).

With regards to the timing and the duration of treatment with antimicrobials, there is limited quality evidence within the literature guiding decision making. Early and aggressive commencement of systemic antimicrobials prior to referral is associated with better short and long term outcomes (Isgren et al., 2020, Rubio-Martínez et al., 2012), however, it is advised to retrieve a synovial sample for culture prior to administration. The ideal number of days to treat with antimicrobials is not well explored within the literature. Several of the retrospective case series show a large range in the duration of treatment of systemic antimicrobials from 1-77 days (Crosby et al., 2019) and 6-54 days (Wright et al., 2003) and some have found that increasing the number of days treated with antimicrobials improves survival (Crosby et al., 2019). This lack of clarity could lead to inappropriately prolonged courses of antimicrobials and is an area that needs further clarification.

Analgesia

Horses with synovial sepsis often present with non-weight bearing lameness and are at a higher risk of developing supporting limb laminitis if left without adequate analgesia. Non-

steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of analgesics and work by reducing pain and inflammation. The mechanism of action of NSAIDs is by inhibition of cyclo-oxygenase enzymes (COX) whose function is to produce prostanoids from arachidonic acid that are important within the inflammatory cascade (Lees and Higgins, 1985). There are two main groups of COX enzymes: COX-1 and COX-2. COX-1 enzymes are produced at a constant rate and are important in the control of physiological conditions such as gastrointestinal barriers. COX-2 enzymes are up-regulated at times of inflammation. The most commonly used commercially available equine NSAIDs, phenylbutazone and flunixin, are non-selective for which COX enzymes they inhibit and therefore in prolonged treatment or after higher dose rates, gastrointestinal side effects can occur, such as right dorsal colitis (Lees and Higgins, 1985). Recently, COX-2–selective inhibitors, such as etodolac, have become available and may potentially decrease the risk of gastrointestinal side effects associated with non-selective NSAIDs (Morton et al., 2005). In an experimental model of equine synovitis, horses treated with etodolac, a COX-2 preferential NSAID, had significant decreases in the synovial WBC and pain (Louro et al., 2021, Morton et al., 2005). Opioids such as morphine and fentanyl can be used to provide analgesia in painful horses, however prolonged treatments have been associated with reduced gastrointestinal motility and faecal output and therefore these parameters should be closely monitored (Boscan et al., 2006). Other adjunctive analgesic techniques such as continuous rate infusions (CRIs), epidurals and local analgesic techniques can be utilised to help control pain. Epidural administration of morphine has been shown to improve recovery from general anaesthesia for horses being treated for synovial sepsis (Louro et al., 2021). In addition, intra-articular administration of morphine has been shown to have an anti-inflammatory effect in experimentally induced acute synovitis (Lindegaard et al., 2010a) and provide analgesia up to 24 hours after intra-articular medication (Lindegaard et al., 2010b).

Outcomes after synovial sepsis

Identification of factors that significantly affect outcome following treatment of synovial sepsis are important to aid clinical case management for veterinarians and owners. A successful treatment can be assessed based on the elimination of infection within the structure, the

survival of the horse, and the return to soundness and athletic function. In a clinical setting, two of the most useful outcomes for case management and owner communication are survival to discharge and the horse returning to athletic function. Between studies, there is wide variation in the reported rates of success after treatment with survival to hospital discharge reported as between 56-100% (Crosby et al., 2019, Findley et al., 2014, Fraser and Bladon, 2004a, Frees et al., 2002, Kidd et al., 2007, Milner et al., 2014, Schneider et al., 1992b, Smith et al., 2006, Taylor et al., 2010, Walmsley et al., 2011, Wereszka et al., 2007, Wright et al., 2003) and return to athletic function 36-94% (Chan et al., 2000, Crosby et al., 2019, Findley et al., 2014, Fraser and Bladon, 2004a, Frees et al., 2002, Kelmer et al., 2012, Lopes et al., 2006, Meijer et al., 2000, Post et al., 2003, Stewart et al., 2010, Taylor et al., 2010, Walmsley et al., 2011, Wereszka et al., 2007, Wright et al., 2003). This variation in the reported success rates could be due to variation in case selection or case management, or due to differences between populations at hospitals. In addition, there are several studies that investigate factors that affect outcomes, however, there is a lack of agreement on the numerous risk factors identified. For example, there are several studies that identify the time from injury to treatment as having a significant effect on outcome (Fraser and Bladon, 2004a, Schneider et al., 1992b,), whereas others have found no significant effect (Frees et al., 2002, Milner et al., 2014, Rubio-Martínez et al., 2012, Smith et al., 2006, Walmsley et al., 2011, Wright et al., 2003). Further investigation into these differences is vital to bring clarity for clinicians on key treatment principles to provide an evidence based approach to case management.

Evidence synthesis review

As identified within this chapter, there are numerous conflicting factors affecting outcomes. Furthermore, the varied publications on synovial sepsis available lend this body of literature to an evidence synthesis review. There are several different types of evidence reviews including structured and subjective reviews (Grant and Booth, 2009). Subjective reviews provide a narrative of the literature available, do not use a set methodology and are often prone to bias (Munn et al., 2018a). Structured reviews follow a strict framework to identify, critique and present the literature (Grant and Booth, 2009). The methodology is repeatable and

transparent to improve the validity of the results obtained and reduce bias. The decision to perform a certain type of review is dependent on the type and number of available studies and the reason for carrying out the literature review. The most commonly used objective literature reviews are systematic reviews and meta-analysis (Munn et al., 2018a). Systematic reviews are considered the gold standard of evidence synthesis, however, they are not as useful for comprehensive mapping and categorising, identifying themes and clarifying concepts of the literature compared to other evidence synthesis techniques (Munn et al., 2018b). Considering the characteristics of the synovial sepsis literature with the varied study designs and the lack of clarity over inclusion criteria, an appropriate alternative evidence synthesis technique to use is a scoping review. A scoping review is similar, but importantly different to a systematic review, as they do not aim to answer a specific question, but instead to provide a map of the evidence available and to help identify and clarify key concepts, and for these reasons it has been chosen as the evidence synthesis method. Importantly, there are currently no structured reviews on the synovial sepsis literature.

Thesis aims and objectives

This thesis aims to produce evidence-based information to influence the clinical decision making for cases and maximise successful outcomes following synovial sepsis. There are three main objectives:

- To objectively examine the current literature and identify and summarise factors that affect treatment success of synovial sepsis
- To report the rate of survival to discharge after surgical treatment for synovial sepsis
- To identify and report risk factors associated with survival

To complete these objectives, a literature review was performed, followed by a prospective study investigating outcomes after surgical treatment of synovial sepsis.

Chapter 2 presents a scoping review of the current evidence on treatment and outcomes following synovial sepsis. This scoping review uses a Preferred Reporting Items for systemic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA – ScR) framework which is an objective and thorough technique to systematically identify and appraise the literature.

Chapter 3 reports the results of a multicentre study investigating long-term survival following synovial sepsis. Ten hospitals were involved and cases of synovial sepsis were recruited over a 15-month period. Cases were then followed up at a minimum of 365 days after surgery to ascertain whether they were alive. Multivariable cox proportional hazard models were used to investigate risk factors associated with poor outcomes.

Chapter 4 concludes the thesis by discussing the results of the previous chapters and identifying key features for practical application and any areas for further research in the future.

CHAPTER TWO

A scoping review of the current evidence on treatment and outcomes following synovial sepsis

Summary Abstract

Background: Synovial sepsis is a frequent cause of morbidity and mortality in horses. Despite advances in diagnostics and treatments persistent infection or chronic lameness can occur.

Objectives: To perform a scoping review to identify and evaluate the current evidence on factors implicated in the success of treatment for synovial sepsis.

Study design: Joanna Briggs Institute scoping review.

Methods: A protocol was registered and a systematic literature search was performed on CAB abstracts, Medline, Scopus and Embase. Inclusion and exclusion criteria were developed and studies systematically reviewed against this. Studies relating to factors affecting treatment success following synovial sepsis were retained and data was extracted on study method, population characteristics and factors significantly associated with treatment outcome.

Results: Two thousand three hundred and thirty-eight studies were identified, and 61 were included to full paper analysis. Eight papers reported significant factors, identifying 15 risk factors associated with two measurements of outcome, either survival and/or return to athletic function. The 15 factors were identified and categorised into pre-, intra- and post-operative factors. Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology, and the use of systemic antimicrobials. There were many discrepancies in inclusion criteria of cases of synovial sepsis as well as measurement and description of outcome variables.

Main limitations: Non-English language studies or conference proceedings were not included. Only small numbers of papers had similar findings.

Conclusions: Standardisation of inclusion criteria is essential to enable comparisons and analysis between studies. Future studies should use methodologies to reduce bias including multicentre and multinational studies, prospective study design, and robust statistical modelling.

Introduction

Synovial sepsis is an important condition affecting the welfare of horses and can result in mortality or loss of athletic performance. In a clinical setting, gold standard treatment aims for the rapid elimination of infection within the synovial structure by early identification, large volume lavage, debridement and systemic and regional antimicrobial use. Previously, studies investigating survival to discharge after synovial sepsis have reported wide ranges of outcomes (56%-100%) (Findley et al., 2014, Milner et al., 2014) (Fraser and Bladon, 2004b, Frees et al., 2002, Schneider et al., 1992b, Smith et al., 2006, Taylor et al., 2010, Wereszka et al., 2007, Wright et al., 2003, Crosby et al., 2019). There is similar variation for reported rates of horses returning to athletic function (36%-94%) (Crosby et al., 2019, Findley et al., 2014, Frees et al., 2002, Post et al., 2003, Smith et al., 2006, Walmsley et al., 2011, Wereszka et al., 2007, Wright et al., 2003). These findings highlight that horses can have a successful outcome, but despite gold standard treatment, there are cases where synovial sepsis leads to death or ongoing lameness, and significant financial implications for owners.

Anecdotally, there appears to be a lack of consensus on how different aspects of synovial sepsis treatment affect outcome. For example, some studies have reported that the duration of clinical signs, prior to referral, significantly affected outcome (Findley et al., 2014, Fraser and Bladon, 2004a, Schneider et al., 1992b) where others found no significant association (Frees et al., 2002, Milner et al., 2014, Rubio-Martínez et al., 2012, Smith et al., 2006, Walmsley et al., 2011, Wright et al., 2003). Similarly, the findings regarding the use of regional antimicrobials are inconclusive with a positive association between use of regional limb perfusion and survival reported in some studies (Rubio-Martínez et al., 2012) and a negative association reported elsewhere (Wright et al., 2003). In addition, different inclusion criteria for synovial sepsis cases and for measurements of treatment outcome are used between research groups (Crosby et al., 2019, Findley et al., 2014, Gilbertie et al., 2018, Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003). Variation in inclusion criteria results in different subsets of horses being given a diagnosis of synovial sepsis and being subsequently investigated making comparisons between study results challenging. This

perceived lack of clarity over key definitions and outcome variables, as well as the broad distribution of publications lends this body of literature to a scoping review.

There are many different types of evidence synthesis reviews that can be used to search, appraise and present the literature including but not limited to systematic reviews, meta-analysis, rapid reviews and scoping reviews (Grant and Booth, 2009). There are currently no structured peer-reviewed articles which describe a systematic search and collation of current evidence investigating synovial sepsis, with only traditional subjective narrative reviews within the literature (Bertone, 2003, Lugo and Gaughan, 2006, Orsini, 2017). Systematic reviews are the most commonly used evidence synthesis technique and are widely used within a human healthcare setting (Munn et al., 2018b). Through structured and transparent searching and analysis of the literature they minimise bias and can provide conclusions which can influence practice and policy (Munn et al., 2018a, Munn et al., 2018b); however, systematic reviews are targeted towards answering a specific question. Where discrepancies in studied populations exist within the literature, or when the number and type of relevant studies is unknown, the usefulness of this evidence synthesis technique is reduced.

A scoping review provides an alternative but similarly objective methodology as well as a broad overview of a specific topic (Tricco et al., 2016). Scoping reviews do not perform any critical analysis of the studies identified, instead through methodological and rigorous peer-reviewed database searching they produce a map of the literature and can identify and clarify key concepts and definitions through extensive charting of data. In addition, they can investigate research conduct and can recognise knowledge gaps in a body of literature (Tricco et al., 2016, Munn et al., 2018b). A scoping review can be performed to assess feasibility and, if then appropriate, to identify specific questions prior to performing a detailed systematic review (Arksey and O'Malley, 2005, Armstrong et al., 2011, Curtis et al., 2019). For these reasons, scoping reviews are gaining popularity as an evidence synthesis tool within equine veterinary research (Clough et al., 2019, Curtis et al., 2019, Egan et al., 2019).

This scoping review aimed to identify and evaluate the current literature available on treatment for synovial sepsis in the horse, including outcomes following different treatment options, and factors associated with the success and failure to respond to treatment. In addition, this scoping review aimed to identify the feasibility and areas appropriate for a future systematic review.

The objectives of this scoping review were:

- To identify the published peer-reviewed literature on treatment for synovial sepsis in the horse through a systematic search of the databases
- To extract and chart key data on study characteristics and results for outcome of synovial sepsis in the horse, including survival and return to work
- To identify any gaps in knowledge in relation to the treatment and outcomes of synovial sepsis
- To categorise and summarise factors that affect treatment success in terms of survival and return to work

Methods and Materials

The Preferred Reporting Items for systemic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) framework was used for this scoping review (Tricco et al., 2018). This review was registered to an existing protocol.[1] All authors and a university librarian provided input and review of the database search strategy. The review was conducted in duplicate by two researchers, one of whom has completed the Joanna Briggs Institute accredited training programme. Any disagreements between the two researchers were decided by a third independent reviewer.

Eligibility criteria

Inclusion and exclusion criteria were created to facilitate assessment and appraisal of the titles, abstracts and studies identified and are described in Table 1. Broad inclusion criteria to capture appropriate literature were used. Horses were included if they were greater than 6 months old as neonates suffering from synovial sepsis have a different pathophysiological process compared to most adult horses who more commonly sustain synovial trauma.

[1] https://osf.io/5sbfk/?view_only=586e7b672deb4342b48da842c9dcb721

Table 1: *Inclusion and exclusion criteria for a scoping review of the literature on synovial sepsis in the horse*

Criteria	Inclusion	Exclusion
Patient	Domesticated adult equids (Horses and ponies)	Donkeys and zebra Foals < 6 months and neonates
Exposures	Synovial sepsis of a bursa, tendon sheath or joint	
Intervention	Either medical or surgical treatment† for synovial sepsis including lavage, systemic or regional antimicrobials, drainage, use of an implant, specific surgical technique.	Papers not relating to treatment
Outcome	Success of treatment – with a focus of either survival‡ and/or return to work§	
Language	English or papers with translation available	Translation not available
Study design	Case series, cohort, case control and cross sectional studies	Narrative, text book chapters, individual case reports
Publication type	Peer reviewed journals Conference proceedings	Unable to obtain full study details Non-peer reviewed journals Papers published before 1980

†Treatment definitions:

Lavage – the washing out of a synovial structure with a fluid.

Systemic antimicrobials –the administration of antimicrobials via intramuscular, intravenous, oral or subcutaneous routes.

Regional antimicrobials – the administration of antimicrobials to a local regional or specific synovial cavity (e.g. intravenous limb perfusion, intra-synovial injection, intra-osseous injection etc.).

Drainage - systematic withdrawal of fluids and discharges from a synovial cavity.

Implant – a material surgically inserted into a tissue for a specific function.

Specific surgical technique – details of a novel or specific treatment technique provided.

‡Survival –included the horse survival to discharge and to other post-operative time points

§Return to work was used as an umbrella term, as decided by the researchers, to include studies relating to any of the following subjective measurements of acceptable function: return to athletic function, return to previous athletic function, return to work

Information sources and search strategy

The initial search strategy was performed on 19th May 2020 and updated on 22nd September 2020 using Medline In-Process & Non-Indexed Citations and Ovid MEDLINE (1946 – present), CAB Abstracts (1973 – present), Scopus Abstract and citation search (1966 – present), and Embase (1974 - present) which include those that are recommended for searching veterinary literature (Grindlay et al., 2012). No date restriction was applied to the search. All references were downloaded and managed in Endnote reference manager (Endnote X9.3.2, Clarivate Analytics).

Search combinations were constructed from the following components using a PICO search strategy:

exp horses/

(horse* or pony or ponies or equine or equidae).mp.

exp sepsis/

(sepsis or septic).mp

exp synovial sheaths/

exp synovial fluid/

exp tenosynovitis/

exp tendon/

exp infection/

infection*.mp

("synovial sepsis" OR "synovial septic" OR "septic arthrit*" OR synovitis).mp.

((infection* or sepsis or septic) adj3 (synovial or tenosynovitis or bursa* or bursitis or tendon* or joint* or synovium or arthritis)).mp

Selection of sources of evidence

The studies were systematically appraised in several steps. Duplicate studies were removed by the primary researcher and titles were assessed by two researchers based on the inclusion and exclusion criteria. Studies were retained if they contained terms relating to outcomes following synovial sepsis, and if this was ambiguous or unclear, the titles were retained to the next stage (abstract review). The abstracts were then independently appraised

based on the inclusion and exclusion criteria outlined in Table 1 by the two researchers separately; these were then discussed, with any ambiguous studies taken forward to full text assessment. The studies taken forward to full text assessment were appraised by one researcher based on the inclusion and exclusion criteria and this was validated by a second researcher to result in a final list of full text studies.

Data charting

The full text studies were analysed and relevant data extracted into charts by the primary researcher. Chart headings, publication categorisation and classification was decided and a consensus reached after discussion with all researchers. Study characteristic data were extracted under the following headings: author, year, geographical location, aims, sample size, treatment investigated, outcomes measured, and significant outcomes. Treatment data were charted into categories if studies described techniques including: lavage, systemic antimicrobials, regional antimicrobials, drainage, use of an implant, specific surgical technique or treatment not specified. Outcomes measured were classified into either survival and/or return to work; if this was not clearly specified within the publication, then it was discussed between the researchers and a category assigned. Those studies with multivariable statistical analysis of outcome variables were grouped and categorised. Following study characteristic analysis, the studies were charted to include synovial structure, inclusion criteria, variable investigated, author, and measure of association. Inclusion criteria were charted to include the number of diagnostic criteria specified, synovial fluid parameters, direct communication with a synovial structure, subjective assessment of cases, and any other details. Case series with no statistical analysis were also categorised dependent on synovial structure, and charted to include synovial structure, author, aims and key findings. No additional methodological quality or risk of bias assessment was performed in line with scoping review protocol (Tricco et al., 2018).

Results

Selection of sources

A total number of 2338 studies were identified on the initial database searches. Figure 1 highlights the flow diagram of publication handling and assessment as outlined in the selection of sources of evidence. There were 111 studies which met inclusion criteria for full text assessment; full text scripts were not available for 15 studies with 12 being abstracts from conference proceedings with no corresponding full text and three were not available. After full text assessment of the remaining studies, nine experimental studies were identified (Bertone et al., 1987a, Bertone et al., 1987b, Bertone et al., 1992, Bertone et al., 1988, Brusie et al., 1992, Chiu Li et al., 2002, Tulamo et al., 1989a, Tulamo et al., 1989b, Whitehair et al., 1992) which induced synovial sepsis and investigated specific treatment techniques or changes in diagnostic parameters over a short period (less than 21 days or not specified). These were excluded from further analysis. Other studies were excluded due to language (10), outcome (4), exposure (3) and intervention (2). There were 61 studies which met the final inclusion criteria and data are presented in Appendix 1 comparing study characteristics, population characteristics as well as significant risk factors identified.

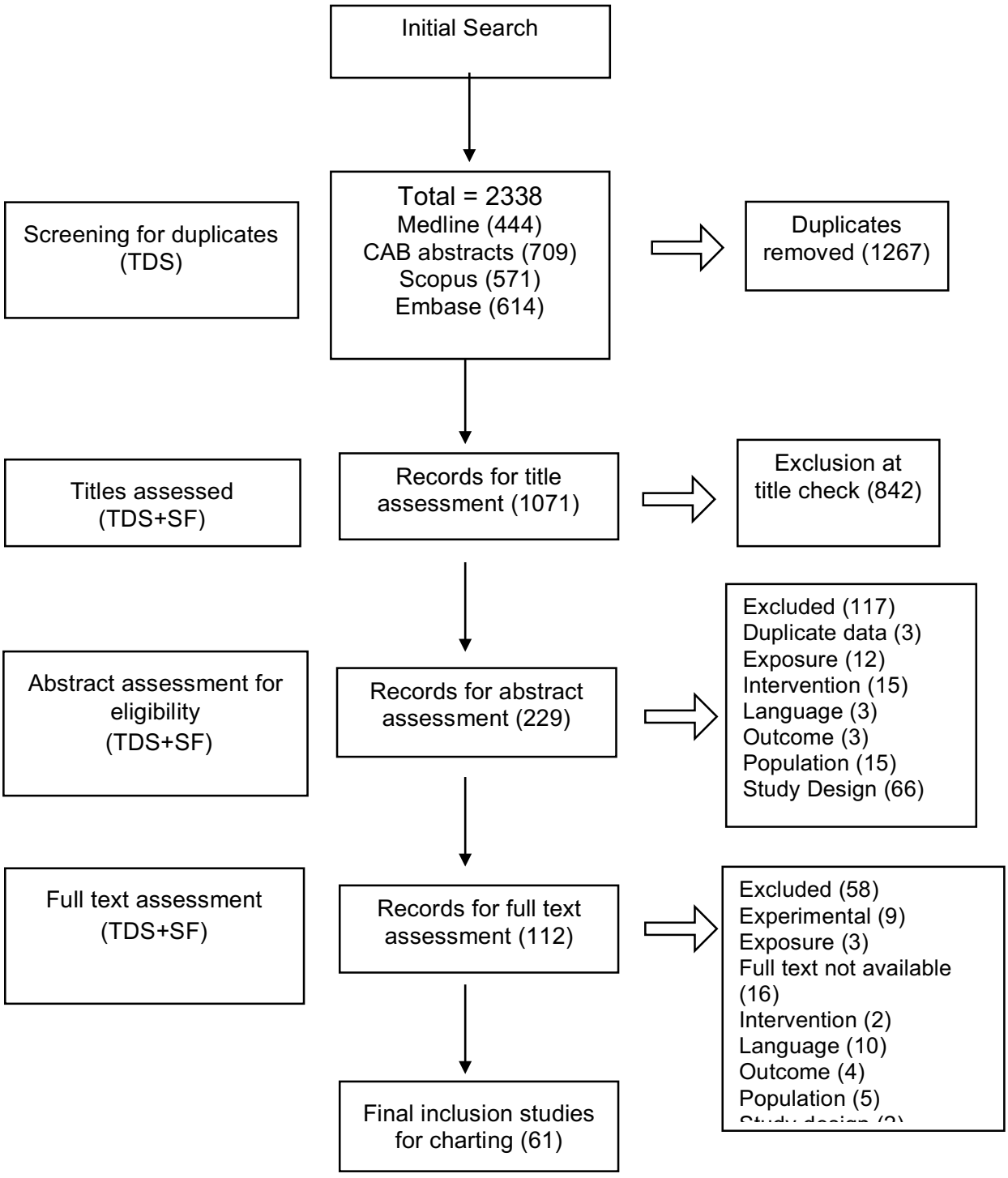

Figure 1: *Flow diagram outlining the process used to identify studies on outcomes after synovial sepsis following systematic review of the available literature. (Initials relate to authors: TDS - Therese de Souza, SF - Sarah Freeman.)*

Characteristics of sources of evidence

From the 61 included studies, there were 23 studies based in the USA, 18 studies based in the UK, four studies based in Australia, three studies based in Belgium and Canada, and two studies based in Egypt. One study was conducted in each of the following countries: Austria, Germany, Israel, Netherlands, Spain, New Zealand and Ireland. Figure 2 demonstrates the case number of the studies, showing that 49/61 (80.3%) studies had between 1 - 60 subjects with 12/61 (19.7%) studies having more than 61 subjects. Most studies were based at one equine hospital (42/61, 68.9%), or two hospitals (9/61, 14.8%), and the remaining studies being based at more than two hospitals (7/61, 11.5%) or not specified (3/61, 4.9%).

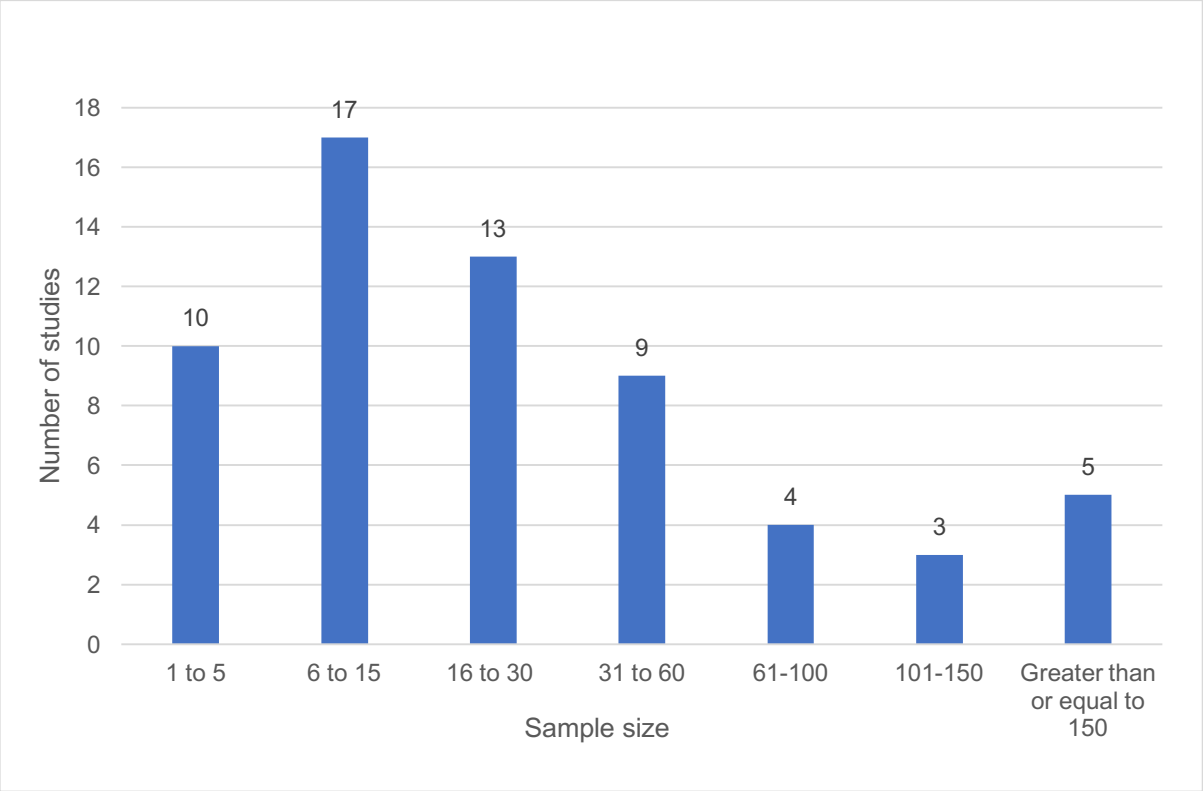

Figure 2: *Chart to show the number of studies with different sample sizes identified for a scoping review of outcomes after synovial sepsis.*

The most frequent type of study designs were retrospective case series (26/61) and retrospective cross-sectional studies (26/61) followed by retrospective cohort (4/61), prospective case series (3/61), prospective observational (1/61) and retrospective case

controlled studies (1/61). Figure 3 demonstrates the different study types plotted dependent on publication date in 5 year ranges.

Of the treatments techniques described within the studies, a combination of lavage, systemic and regional antimicrobials was described in 54/61 studies and lavage and drainage was described in 20/54 of these studies. A specific surgical technique or surgical implant was described in 21/61 and 13/61 studies.

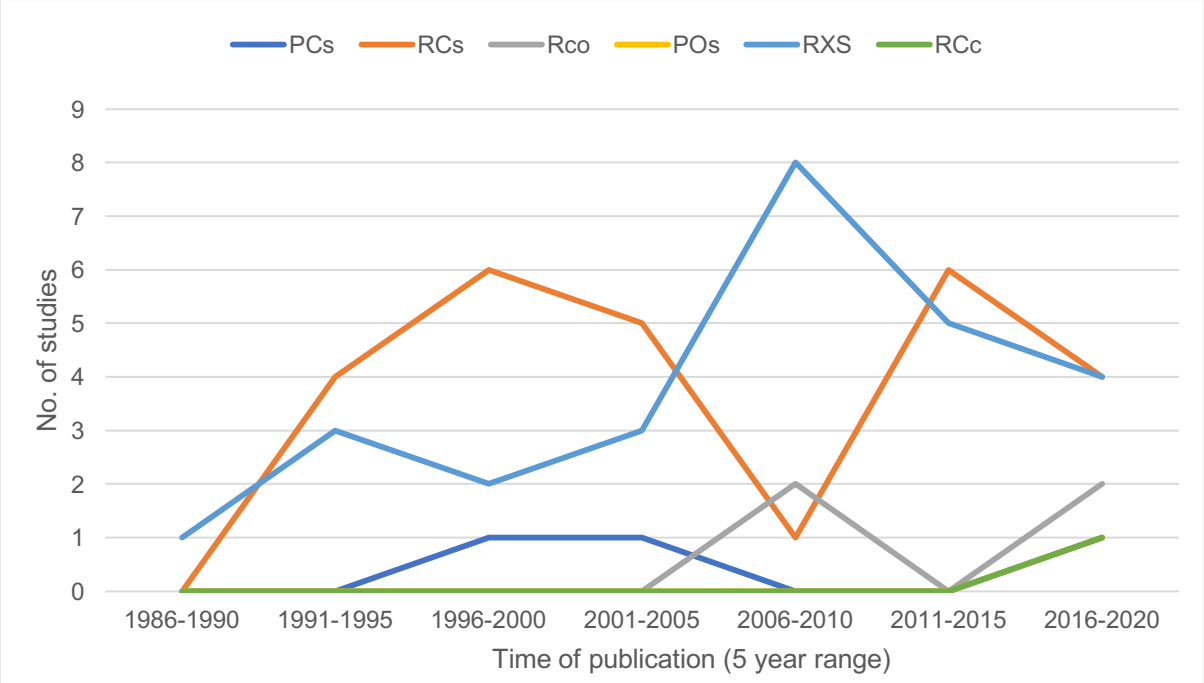

Figure 3: *Chart to show the trend of different publication types of the studies identified from a scoping review of outcomes after synovial sepsis between the years 1986-2020. (Abbreviations: PCs – Prospective case series, RCs – Retrospective case series, Rco – Retrospective cohort study, POs – prospective observational study, RXS – retrospective cross-sectional study, RCc – Retrospective case controlled study.)*

Within these 61 studies, eight investigated outcomes following synovial sepsis using multivariable analysis. The inclusion criteria of these 8 studies and the reported results are presented in Table 2 and 3 respectively. Eighteen studies did not utilise a multivariable analytical approach, but used different statistical analysis (15/18) to investigate outcome and

the results are presented in Appendix 3. Three studies (3/18) found no statistically significant data on outcome and were not included (Meagher et al., 2006, Lopes et al., 2006, Smith et al., 2006). Descriptive case series that reported outcomes on specific causes, treatment techniques or specific synovial structures are presented in Appendix 2.

Other small groups and themes of studies were identified. There were six studies that investigated the prevalence of synovial sepsis after iatrogenic intervention and reported the outcome of these horses (Borg and Carmalt, 2013, Brunsting et al., 2018, Hawthorn et al., 2016, Lapointe et al., 1992, Olds et al., 2006, Stöckle et al., 2018). All six studies had small numbers of horses (range 3-16) and no statistical analysis was performed on outcome for any of the studies. One study specifically described treatment for horses with blackthorn synovitis (Ashton, 2018) and one study identified outcomes in working equids (Gamal et al., 2010).

Results of individual sources

Eight studies investigated outcome following synovial sepsis using multivariable analysis and Table 2 presents the inclusion criteria specified within the eight studies. One study included descriptive details of the diagnosis of synovial sepsis (Wright et al., 2003). Seven studies specified different values of synoviocentesis parameters for the diagnosis of cases of synovial sepsis including the white blood cell count (range 5-30 x 10^9 cells/L), with five of these studies further specifying a percentage of polymorphonuclear cells (80-90%) (Crosby et al., 2019, Isgren et al., 2020, Milner et al., 2014, Rubio-Martínez et al., 2012, Wereszka et al., 2007) and six studies identified different total protein concentrations (range 20-40g/L) (Crosby et al., 2019, Findley et al., 2014, Isgren et al., 2020, Milner et al., 2014, Rubio-Martínez et al., 2012, Wereszka et al., 2007). Five studies identified a positive bacterial culture (Crosby et al., 2019, Isgren et al., 2020, Milner et al., 2014, Rubio-Martínez et al., 2012, Wereszka et al., 2007), two identified cytological features of bacteria colonisation (Isgren et al., 2020, Rubio-Martínez et al., 2012). One study separated horses with "fresh intra-synovial lacerations with minimal contamination" from horses with established synovial sepsis (Rubio-Martínez et al., 2012), whereas confirmation of synovial involvement was a criterion of inclusion for others (Crosby et al., 2019, Findley et al., 2014, Isgren et al., 2020, Milner et al., 2014).

The treatment techniques involved lavage, systemic and regional antimicrobials in six of eight studies (Crosby et al., 2019, Findley et al., 2014, Isgren et al., 2020, Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003). In one study a specific surgical technique of regional limb perfusion was described (Rubio-Martínez et al., 2012). Treatment techniques were not specified in one paper (Gilbertie et al., 2018). The outcome measured for all eight studies was survival to hospital discharge with or without including return to athletic function. The timeframe of follow up differed between the studies; two studies looked at survival without residual lameness (Gilbertie et al., 2018, Milner et al., 2014), whereas six studies had a range of follow up times between three months and 16 years post operatively. Three studies used an objective measurement of outcome using race records either solely or in combination with telephone questionnaires (Crosby et al., 2019, Isgren et al., 2020, Wright et al., 2003) with three other studies using only telephone questionnaires to owners, trainers or

referring veterinarians for follow up (Findley et al., 2014, Rubio-Martínez et al., 2012, Wereszka et al., 2007).

Table 3 demonstrates the 15 risk factors that were found to be statistically significant evidence of association including: horse factors, synovial structure, type of injury, duration of clinical signs prior to referral, treatment prior to referral, synovial fluid analysis pre-operatively, presence of pannus, tendon injury, bone pathology, number of surgeries, surgical factors, lavage technique, regional antimicrobials, systemic antimicrobials, synovial fluid analysis post-operatively. Table 4 highlights the number of studies within each category of risk factor divided into pre-operative (n=6), intra-operative (n=6) and post-operative factors (n=3).

Table 2: *Inclusion criteria specified by the studies which reported risk factors affecting outcome after synovial sepsis in the horse*

Author	Number of criteria specified	Synovial fluid analysis						Wound/direct communication	Subjective assessment	Other details
		Gross appearance of SF	Nucleated cell count	% of PMN	Total protein concentration	Positive bacterial culture	Cytological examination			
Crosby *et al*.	X	X	≥ 30 x 10^9 cells/L	>80%	≥ 30 g/L	√	X	√	X	
Findley *et al*.	X	X	>20 x 10^9 cells/L	X	>20 g/L	X	X	√	X	
Gilbertie *et al*.	X	X	>10,000 cells/μL	X	X	X	X	X	√	Supprative or fibrinous inflammation at PME
Isgren *et al*.	≥1 of the following†	X	≥ 10 x 10^9 cells/L	>80%	>30 g/L	√	Intracellular bacteria	√	X	
Milner *et al*.	X	X	≥ 5 x 10^9 cells/L	>80%	>30 g/L	√	X	√	X	
Rubio Martinez *et al*.	≥ 3 of the following	X	>30,000 cells/μL	>90%	>4g/dL	√	Organisms present, degenerative changes to PMN	X	X	
Wereszka *et al*.	X	X	>30,000 cells/μL	>90%	>4 g/dL	√	X	X	X	Clinical parameters suggestive of synovial sepsis (lameness, heat, effusion of DFTS, surgical findings)
Wright *et al*.	X	√	√	X	√	X	X	√	X	

Abbreviations: √ = Included inclusion criteria, X = not specified, PME – post mortem examination, DFTS – digital flexor tendon sheath, SF – synovial fluid, PMN – polymorphonuclear leukcocytes, † - needed all SF parameters to be elevated to count as 1 of the criteria.

Table 3: *Key findings of studies which reported risk factors affecting outcome after synovial sepsis in the horse*

Risk factor	Structure or type of injury if specified †	Author	Measures of association (multivariable analysis)
Horse factors	Nail penetration	Findley *et al*. (2014)	Group 2 breeds (Thoroughbred/Thoroughbred crosses, Warmbloods/Warmblood crosses and Arabs) were less likely to return to the pre-injury level of activity than Group 1 breeds (cobs, ponies, draught breeds and draught breed crosses) (OR 32.1, 95% CI 2.2-135.4, P=0.001)
		Rubio Martinez et al. (2012)	Mares were more likely to survive than geldings (OR 9.814, 95% CI, 1.798-53.559, P=0.03), and intact males were more likely to survive than geldings (OR 5.33, 95% CI, 0.619- 45.9, p=0.03).
		Wright *et al*. (2003)	In horses that survived, non-Thoroughbred horses had significant associations with reduced post-operative performance compared to Thoroughbreds and Thoroughbred-X (OR 6.256 95% CI 1.248–31.371 P= 0.026)
Synovial structure (s)		Rubio Martinez *et al*. (2012)	The probability to return to performance at a level equal to or higher than before the injury was higher for horses in which the hind limb was involved, compared with those in which the forelimb was involved (OR 16.44, 95% CI 1.71- 110.23, P= 0.028).
		Rubio Martinez *et al*. (2012)	Horses with a single synovial structure involved were more likely to survive long-term than horses with multiple synovial structures (including synovial tendon sheaths, bursae and joints) involved (OR 6.205, 95% CI 1.168-32.952, P= 0.032).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka *et al*. (2007)	Horses with sepsis of an adjacent joint were less likely to survive at least 1 year after surgery, compared with horses without evidence of sepsis of an adjacent joint (OR 0.131, 95% CI 0.015-0.0947, P< 0.044).
		Wright *et al*. (2003)	In horses that survived, a combination of synovial structure involvement had significant associations with reduced post-operative performance compared to single synovial involvement (joint, tendon sheath, bursae) (OR 7.250 95% CI 1.244–42.259, P=0.028).
Injury	Nail penetration	Findley *et al*. (2014)	Direct penetration of the central sulcus of the frog was associated with euthanasia during hospitalisation (OR 10, 95% CI 1.9–51.8, P=0.002).
		Milner *et al*. (2014)	Presence of a wound on admission was associated with increased likelihood of survival (OR 4.75, 95% CI 1.21–18.65, P=0.02).
Duration of clinical signs prior to referral	Nail penetration	Findley *et al*. (2014)	Increasing number of days to presentation was significantly associated with failure to return to pre-injury level of athletic function (OR 1.1, 95% CI 1.1-1.6, P<0.0001)
	Nail penetration	Findley *et al*. (2014)	Increasing number of days from injury to presentation was associated with euthanasia during hospitalisation (OR 1.2, 95% CI 1.0-1.3, P=0.006)
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka *et al*. (2007)	Horses in which duration of clinical signs was < 1 day were significantly more likely to survive at least 1 year after surgery, compared with horses in which duration of clinical signs was > 10 days (OR 15.6, 95% CI 1.24–500, P<0.027).

Treatment prior to referral	Calcaneal bursae	Isgren *et al*. (2020)	The administration of systemic antimicrobials prior to referral was associated with reduced mortality (HR 0.25, 95% CI 0.11–0.60, P = 0.002).
Synovial fluid analysis pre-operatively		Gilbertie *et al*. (2018)	Increased likelihood of euthanasia significantly associated with coagulase positive Staphylococcus spp. (OR 7.66, 5.46–10.74, P < 0.0001), β-hemolytic Streptococcus spp. (OR 5.18, 3.56–7.55, P < 0.0001), Enterococcus spp. (OR 18.38, 11.45–29.52, P = 0.002), Enterobacteriaceae (OR 31.37, 22.28–44.17, P < 0.0001), Pseudomonas aeruginosa (OR 9.31, 5.30–16.34, P = 0.0004) or other gram-negative species (OR 3.51, 2.07–5.94, P = 0.001)
		Gilbertie *et al*. (2018)	Increased likelihood of euthanasia significantly associated with infections by gram-negative organisms (OR 5.03, 3.77–6.72, P < 0.0001)
		Gilbertie *et al*. (2018)	Increased likelihood of euthanasia significantly associated with multi-drug resistance (MDR) (OR 16.11, 12.09–21.45, P < 0.0001)
		Gilbertie *et al*. (2018)	Increased likelihood of euthanasia for MDR gram-positive organisms (OR 1.85, 1.21–2.81, P < 0.005) and gram-negative organisms (OR 119.24, 70.57–201.46, P< 0.0001)
		Milner *et al*. (2014)	Higher synovial fluid TP levels measured on admission were associated with a reduced likelihood of survival (OR 0.88, 95% CI 0.83–0.94, P<0.001).
Presence of pannus		Milner *et al*. (2014)	Horses with evidence of moderate/severe synovial inflammation identified during endoscopic examination were around 4 times less likely to survive to discharge than horses with no synovial inflammation (OR 0.28, 95% CI 0.12–0.67, P= 0.004).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka *et al*. (2007)	Presence of severe pannus was significantly associated with a decreased likelihood of returning to a previous or higher level of performance (OR 0.067, 95% CI 0.010–0.455, P< 0.006).
		Wright *et al*. (2003)	For horses which returned to performance, the presence of pannus had significant associations with reduced post-operative performance and non-survival (OR 2.839, 95% CI 1.013-7,995, P=0.047)
		Wright *et al*. (2003)	Presence of marked pannus was significantly associated with non-survival compared to moderate/minor or no pannus (OR 5.487, 95% CI 1.081-27.854, P=0.040)
Tendon injury	Calcaneal bursae	Isgren *et al*. (2020)	Moderate/severe tendon involvement (≥30% cross sectional area) was associated with increased mortality (HR 7.95, 95% CI 3.33–19.0, P<0.001).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka *et al*. (2007)	Horses with partial or complete tendon rupture were significantly less likely to survive at least 1 year after surgery, compared with horses without evidence of tendon rupture (OR 0.064, 95% CI 0.003-0.554, P<0.026).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka *et al*. (2007)	The presence of tendon injuries (Fraying or tearing of the tendon seen during surgery or tendonitis diagnosed ultrasonographically) (OR 0.094, 95% CI 0.013–0.674, P< 0.019) were significantly associated with a decreased likelihood of returning to a previous or higher level of performance.
Bone pathology	Nail penetration	Findley *et al*. (2014)	Concurrent injury to the pedal bone was associated with euthanasia during hospitalisation (OR 32.1, 95% CI 2.6–101.9, P=0.005).

		Wright *et al*. (2003)	Presence of osteochondral pathology was significantly associated with non-survival (OR 6.38, 95% CI 1.31-31.03, P=0.022)
		Wright *et al*. (2003)	Presence of osteomyelitis was significantly associated with non-survival (OR 6.259, 95% CI 1.651-23.654, P=0.007)
Number of surgeries	Nail penetration	Findley *et al*. (2014)	More than one surgery was significantly associated with failure to return to pre-injury level of athletic function (OR 5.6, 95% CI 1.0-32.7, P=0.03)
		Milner *et al*. (2014)	Horses undergoing greater than one endoscopic procedure were around 5 times less likely to survive to hospital discharge (OR 0.19, 95% CI 0.05–0.70, P=0.005).
Surgical factors	Nail penetration	Findley *et al*. (2014)	The hospital at which the horse was treated was associated with failure to return to the pre-injury level of athletic function (OR 2.9, 95% CI 0.6-14.6, P<0.0001) (OR 0.5, 95% CI 0.003-0.8, P<0.0001) (OR 1.4, 95% CI 0.2-9.9, P<0.0001)
	Nail penetration	Findley *et al*. (2014)	The hospital at which the horse was treated was associated with euthanasia during hospitalisation (OR 0.1, 95% CI 0.3-0.9, P=0.006) (OR 0.2, 95% CI 0.02-0.8, P=0.006) (OR 0.01, 95% CI 0.007-0.4, P=0.006).
		Milner *et al*. (2014)	Anaesthetic induction during normal working hours was associated with increased likelihood of survival (OR 0.36, 95% CI 0.15–0.88 P=0.02). Horses undergoing anaesthetic induction outside of normal working hours were around 3 times less likely to survive to hospital discharge.
Lavage technique		Rubio Martinez *et al*. (2012)	Horses that were not treated with intra-synovial continuous lavage with isotonic fluids were more likely to return to the same or higher level compared with those in which ISCL with isotonic fluids was used (OR, 43.99, 95% CI, 1.929 to > 999.999; P = 0.018).
Regional antimicrobials		Wright *et al*. (2003)	For horses which returned to performance, the use of regional IV antimicrobials had significant associations with reduced post-operative performance and non-survival (OR 3.192, 95% CI 1.085-9.394, P=0.035)
		Wright *et al*. (2003)	In horses that survived, use of regional IV antimicrobials had significant associations with reduced post-operative performance compared to not using regional IV antimicrobials (OR 4.256 95% CI 1.056–17.153, P=0.042)
Systemic antimicrobials		Crosby *et al*. (2019)	For return to function when considering each individual synovial structure, treatment with doxycycline was negatively associated with return to function (OR 0.39, 95% CI 0.19–0.8, P = 0.031).
		Crosby *et al*. (2019)	Increasing number of days of treatment with systemic antimicrobials was associated with increased likelihood of survival for each horse (OR 1.15, 95% CI 1.04−1.27, P = 0.025) and when considering each individual synovial structure (OR 1.11, 95% CI 1.04−1.17, P = 0.004).
		Rubio Martinez *et al*. (2012)	Higher long-term survival rates for horses that received systemic antimicrobials prior to admission compared to those that did not receive systemic antimicrobials (OR,11.89, 95% CI 2.017-70.181, P=0.006).
		Wright *et al*. (2003)	For horses which returned to performance, the duration of systemic antimicrobials > 7 days had significant associations with reduced post-operative performance and non-survival (OR 13.960, 95% CI 1.786-109.133, P=0.012)

	Wright *et al*. (2003)	For horses which returned to performance, the use of systemic antimicrobials > 12 days had significant associations with reduced post-operative performance and non-survival (OR 15.429, 95% CI 1.891-125.862, P=0.011)
Synovial fluid analysis post-operatively	Milner *et al*. (2014)	Synovial fluid TP value measured post operatively was significantly associated with survival (likelihood of survival decreasing as TP values increased) (OR 0.94, 95% CI 0.90–0.98, P = 0.013).

Abbreviations: ANOVA – Analysis of variance, CI – confidence interval, DFTS – digital flexor tendon sheath, HR – hazards ratio, ISCL – intra-synovial continuous lavage, IV – intravenous, MDR – multidrug resistance, OR – odds ratio, TP – total protein. † If structure or nature of injury not specified it relates to general synovial structures (which can include joints, tendon sheaths and bursae) caused by a range of inciting causes.

Table 4: *Summary of studies reporting significant risk factors affecting treatment outcome after synovial sepsis*

	Risk factor type	Number of studies
Pre-operative	Horse factors	2
	Cause of injury	2
	Synovial structure involved	3
	Synovial fluid analysis	2
	Treatment prior to referral	1
	Duration of clinical signs prior to referral	2
Intra-operative	Bone pathology	2
	Tendon pathology	2
	Presence of pannus	3
	Surgical factors	2
	Lavage	1
	Number of surgeries	2
Post-operative	Systemic antimicrobials	3
	Regional antimicrobials	1
	Post-operative synovial fluid analysis	1

Discussion

This scoping review has identified the pertinent and current literature available on treatment for synovial sepsis and found a varied group of sixty-one studies from fourteen countries. From these sixty-one studies, eight have been identified that report significant risk factors and outcome. Within this body of literature, key issues that have been identified include the lack of consistency in inclusion criteria and follow up duration and measurement of outcome between studies, and the small number of studies that identify significant risk factors.

Summary of evidence – Research conduct

Definitions

"To advance knowledge of a clinical entity, we must begin with a definition" (Kaliner et al., 2009). Refining inclusion criteria for horses with synovial sepsis is a difficult undertaking as it is a broad term used to describe a dynamic pathological process of a vast range of clinical presentations. There are currently no evidence based recommendations for inclusion criteria or diagnosis for cases of synovial sepsis. Of the eight studies identified within this scoping review that report risk factors affecting outcome after synovial sepsis, there were marked differences in the diagnostic criteria for synovial fluid 'cut-off' parameters, and there was varied differentiation and separation of contaminated or infected synovial structures. By using different definitions, this resulted in different subsets of horses being included and investigated under an umbrella term of synovial sepsis, making comparisons of results between studies impossible. Previous scoping reviews have identified this issue within different bodies of literature and acknowledge that variability identified in inclusion criteria of study subjects can restrict the ability to conduct systematic reviews (Hines et al., 2017). Establishing agreement with inclusion criteria is a common issue within research settings. In human literature, consensus methods are often used to provide guidelines regarding key features of pathology and treatment, as well as creating diagnostic criteria for specific diseases (Kwong et al., 2016, Nair et al., 2011). Consensus methods include techniques such as nominal group processes, consensus development panels, and Delphi techniques, and are based on evidence based medicine. If this is not available then recommendations are based on knowledge and expertise of specialists through a set protocol of discussion (Kwong et al., 2016, Waggoner et al., 2016). Their findings should be frequently reviewed in order to adapt

with changing evidence and practice (Nair et al., 2011). There are several consensus statements within veterinary scientific writing which provide guidelines and recommendations to other practitioners and researchers for specific diseases (A.G. Boyle 2018, ECEIM, 2021, Sykes B.W. et al., 2015). There is currently no consensus statement for synovial sepsis and this could significantly improve future research if clarity and agreement over inclusion criteria could be implemented.

Measurement of Outcome

There were key differences identified in the measurement of outcome variables. The main measurements of outcome after synovial sepsis were survival to hospital discharge and/or return to athletic function (Appendix 1). Of the studies that looked at return to athletic function, this was defined differently. Some studies looked at survival without residual lameness (Gilbertie et al., 2018, Milner et al., 2014), whereas others tried to quantify the level at which the horse was working either subjectively with telephone questionnaires (Findley et al., 2014, Rubio-Martínez et al., 2012, Wereszka et al., 2007) or objectively in combination with online race records (Crosby et al., 2019, Isgren et al., 2020, Wright et al., 2003). Cook *et al*., has proposed a set of definitions reporting outcomes for clinical orthopaedic trials and suggests using the terms return to 'full function', 'acceptable function', and 'unacceptable function' (Cook et al., 2010). This framework, if implemented, could provide guidance for authors as well as consistency between studies. There were also differences in the time frame of 'long term' follow up and the method of follow up between studies. There was a large range in the follow up duration between studies from three months to 16 years post-operatively. Defining and stating the duration of follow up more transparently and implementation of standardised time frames would make interpretation of outcome measurements clearer. Again, the lack of consistency means consolidation of the evidence and interpretation of studies investigating return to athletic function remains challenging and further evidence synthesis, including a systematic review, is not possible.

Study design and conduct

Study design features that were identified as limiting the quality of evidence included the small number of studies that accounted for confounding variables, the lack of treatment

details described within the materials and methods, and the small sample sizes. Within the 61 studies, 18 cross-sectional studies were identified that investigated outcomes following synovial sepsis which did not account for confounding factors within their statistical analysis (Appendix 3). Only eight studies were identified to take into consideration confounding factors and used multivariable analysis. Multivariable analysis is an essential statistical tool to enable complex relationships to be established between several variables and should be utilised in studies where study design is unable to account for confounding bias (Moola S and Lisy K, 2020, Pourhoseingholi et al., 2012).

In addition, adequate details of treatment techniques were often lacking. Of the eight studies identifying significant factors affecting outcome, six of eight described some form of treatment technique involving lavage, systemic and regional antimicrobials with one study not specifying any treatment techniques used at all. Significant details of surgical techniques including wound resection and closure, synovial resection, lavage fluid and volume or drainage could be important variables affecting treatment outcome. This can be accounted for if the studied population all receive the same treatment, and this is clearly stated during the study design process; however, if these are not controlled nor described then further details of treatment techniques should be included within the results to allow comparisons and improve the external validity of the research. This is a common finding within the studies identified and may be due to the retrospective nature of the study design, with data being collected from clinical case records. This could be improved in the future by standardised reporting and inclusion of clear descriptions of surgical techniques either within the study design or results. In addition, the use of prospective study designs investigating these factors could be of benefit to assessing confounding variables.

Sample size is a common limitation of veterinary and human research (Thorlund and Mills, 2012). This scoping review identified that within the 61 studies initially identified, 80% of the studies had less than 60 subject participants. Of the eight studies that identified specific risk factors, one contained less than 60 subjects (Wereszka et al., 2007) and seven included more than 61 subjects. The power of a study increases with sample size (Howick, 2009 and

2011, Thorlund and Mills, 2012). This is applicable to investigating outcomes after synovial sepsis when differences between outcomes are small. Death after treatment of synovial sepsis is relatively infrequent and the differences between horses reaching a better or worse level of athletic function are likely to be small and multifactorial. Larger sample sizes can improve the ability to detect small differences or investigate multiple variables and can facilitate more robust statistical modelling, thereby improving the quality of the data (Faber and Fonseca, 2014, Hulley, 2007). Most studies investigated data from a single hospital (68.9%), with only seven studies investigating data from three or more hospitals, which likely contributed to the small number of study participants. Multicentre and multinational studies provide both access to a larger sample size increasing the ability to detect small differences as well as providing greater variety of the population studied, enabling the results to be applicable to the general population (Oakley et al., 2012).

Summary of Evidence – key findings and factors identified

The findings from the small number of studies with similar risk factors were categorised into three groups, and this identified that there were six pre-operative, six intra-operative and three post-operative risk factors. Within these categories, the most commonly represented risk factors were the number of synovial structures involved (Rubio-Martínez et al., 2012, Wereszka et al., 2007, Wright et al., 2003), the presence of pannus (Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003), presence of tendon and bone pathology (Findley et al., 2014, Isgren et al., 2020, Wereszka et al., 2007, Wright et al., 2003), and the use of systemic antimicrobials (Crosby et al., 2019, Rubio-Martínez et al., 2012, Wright et al., 2003,).

Although no risk assessment was performed, this scoping review identified themes within these studies. Interestingly, from those studies that investigated all synovial structures (including tendon sheaths, bursae, and joints), no specific synovial structure was reported to have a worse or better prognosis. However, three studies found that horses with injuries involving multiple synovial structures had a reduced likelihood of survival (Rubio-Martínez et al., 2012, Wereszka et al., 2007, Wright et al., 2003). In addition, five studies identified that more severe injuries with concurrent tendon injury (Isgren et al., 2020, Wereszka et al.,

2007), bone pathology (Findley et al., 2014, Wright et al., 2003), or presence of moderate to severe pannus (Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003) were significant negative prognostic indicators for both survival and return to work. However, establishing detailed criteria and grades for different tendon, bone and synovial pathology is necessary to further determine the nuances of these associations.

The use of systemic antimicrobials was found by three studies to affect survival and return to work (Crosby et al., 2019, Rubio-Martínez et al., 2012, Wright et al., 2003). Rubio-Martinez *et al*. found horses that received systemic antimicrobials prior to admission had higher survival rates compared to those that did not. This finding has not been previously reported and suggests that early intervention can improve outcomes. Crosby *et al*. found that the use of a specific antimicrobial, doxycycline, was associated with a negative outcome. The authors suggested that doxycycline was used for refractory cases in their population. This may have skewed its use for cases that had not responded to initial broad spectrum antimicrobials. The presence of a wound communicating with the synovial structure was found to be a factor associated with better survival (Milner et al., 2014). One hypothesis from the authors was that this was due to earlier identification of wounds by clients compared to more insidious causes of synovial sepsis which may allow earlier implementation of treatment (Milner et al., 2014). All eight of the studies in Table 3 investigated how timing of the injury prior to referral affected outcome. Surprisingly, only two studies found a significant association with duration of injury prior to referral with a poorer prognosis for survival and return to work (Findley et al., 2014, Wereszka et al., 2007). It is anecdotally believed that there is a ‘golden’ window in which treatment for synovial sepsis carries a greater chance of success; however, there is a lack of robust evidence within this body of literature to support this impression. Early recognition of wounds, increased awareness of synovial structures and implementation of treatment is undeniably desirable and further research into owners and vets initial triage of potential synovial sepsis cases is important to further quantify these associations.

This scoping review highlights that only a small number of studies have found associations with similar risk factors, which would make these associations difficult to analyse with a

systematic review; however, themes that have been identified and could warrant future investigation include how early recognition influences the early implementation of antimicrobial treatment, bone and tendon involvement, and intra-synovial pannus formation.

Limitations of the scoping review

There are several inherent limitations to the scoping review process. A scoping review does not provide analytical critique of the literature compared to a systematic review, nor does it specifically answer a research question (Munn et al., 2018a). It can provide an overview without specific details or assessment of risk within the published work and identify bodies of evidence for more detailed analysis through a systematic review (Munn et al., 2018a). Broad search terms and inclusion criteria were used to capture as many of the appropriate studies as possible using the key veterinary research databases including Medline, CAB abstracts and Scopus (Grindlay et al., 2012) which were outlined in the a priori protocol; however, this search strategy did not identify some studies which would have met the inclusion criteria, and had been identified by a hand search of the references of the included studies. An additional search engine, Embase, was included after the initial searches, which allowed further studies to be captured likely due to differences in indexing and inclusion of additional journals (Grindlay et al., 2012). Quality control check points for search strategies should be implemented in scoping reviews, or independent assessment to ensure an appropriate breadth and representative literature is captured.

Conference proceedings and full texts not in English language where no translation was available were excluded. Conference proceedings offer an important source of new data often prior or exclusive to publication elsewhere, with some studies suggesting less than 10% of conference proceedings being subsequently published (Brace et al., 2010). In addition, there may be a selection bias for conference proceedings with positive results to be subsequently published and therefore the results of conference proceedings may offer a true representation of both positive and negative results (Sargeant and O'Connor, 2020). An extensive search strategy was performed to gain access to the full papers; however, 15 studies were not

available, 12 of which were abstracts from conference proceedings. It could benefit future work if conference proceedings were more widely accessible with effective dissemination.

Several steps were taken to reduce bias and subjectivity within the methodology. An a priori protocol was developed and inclusion and exclusion criteria developed after collaborative discussion between authors. The search terms used were developed by the authors with consultation from an experienced librarian to help with specific database nuances. Systematic assessment of the studies was performed independently by two authors, with any ambiguous titles or abstracts being taken through to the next round of assessment; however, the charting process was performed by one author and verified by all others, which could have led to selection bias. It has been suggested to use two authors to independently chart all texts and to discuss any discrepancies that could reduce this selection bias in the future (Rose et al., 2017, Tricco et al., 2016).

Scoping reviews can act as an evidence synthesis tool, as well as providing an evidence based precursor to performing a systematic review. At this stage, although no further critical analysis of the relevant risk factors was presented, the limited number and poor compatibility between studies would mean a systematic review would not be possible as an additional evidence synthesis tool. This is a common conclusion of scoping reviews; Tricco *et al*. found only 12% of scoping reviews included a recommendation of a systematic review in their conclusions (Tricco et al., 2016).

Conclusion and recommendations

This scoping review has extracted and categorised the current evidence relevant to treatment outcomes after synovial sepsis to aid clinicians, and to inform future research.

Key future research recommendations include:

- The development of standardised inclusion criteria for cases of synovial sepsis and more comparable measurements of outcome are essential for more detailed evidence synthesis of this body of literature to occur
- Use of methodologies to reduce bias including multicentre and multinational studies, prospective study design, and robust statistical modelling
- Standardised reporting of treatment techniques within study design descriptions
- Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology, and the use of systemic antimicrobials.
- Future areas of research are important to establish criteria and grades for different tendon, bone and synovial pathology and to assess the effect of early recognition of synovial sepsis and implementation of treatment on desirable outcomes.

APPENDIX TO CHAPTER TWO

Appendix 1*: Study characteristics of the 61 studies identified describing in a scoping review investigating factors implicated in treatment success following synovial sepsis*

Author (year)	Country	Study type	Study population (no. of centres)	Aims of study	Treatment investigated †							Sample size (no. horses fitting inclusion criteria)	Outcomes measured		Significant factors identified
					Lavage	Systemic ABs	Regional ABs	Drainage	Implant	Specific surgical technique	Not specified		Survival	Return to athletic activity	
Ashton (2018)	UK	PCs	Referral hospital (1)	To describe the presentation, diagnosis, treatment and outcome of blackthorn synovitis.	√	√				√		35(35)	√	√	No significant factors identified.
Bergstrom *et al*. (2020)	USA	RCs	University teaching hospitals (2)	to describe the case details, clinical findings, treatment and outcomes of 10 horses with complex pastern injuries involving the scutum medium.						√	√	10 (3)	√	√	No significant factors identified.
Booth et al. (2004)	UK	PCs	University teaching hospitals (3)	To describe and evaluate a technique for radical resection of the entire intrathecal component of the CDET in horses.	√	√		√		√		7(7)		√	No significant factors identified

Booth *et al.* (2001)	UK	RCs	Not specified	To describe the treatment of septic small tarsal joints with gentamicin-impregnated PMMA beads.	√	√	√		√	√		11(11)	√	√	No significant factors identified
Borg and Carmalt (2013)	Not specified	RCs	Type of hospital not specified (1)	To investigate whether routine elective arthroscopic surgery in horses without antimicrobial prophylaxis results in a higher rate of septic arthritis than for horses with prophylactic antibiotic administration.	√	√	√					444(3)	√	√	No significant factors identified
Brungsting *et al.* (2018)	Belgium	RCs	Referral hospital (1)	To evaluate the incidence of SSI and septic arthritis following elective arthroscopy and to identify associated risk factors for SSI and septic arthritis							√	1079(12)	√	√	No significant factors identified
Butson *et al.* (1996)	UK	RCs	Mixed referral centres (>1)	To describe the use of gentamicin-impregnated PMMA beads and as an adjunctive treatment for synovial sepsis after conventional treatment has failed or there is evidence of osteomyelitis.	√	√	√		√	√		12(12)		√	No significant factors identified

Byrne *et al.* (2020)	Australia	RCs	Referral hospital (1)	To describe the presentation, features, surgical findings, treatment and long-term outcome of synovial sepsis of unknown origin in adult Thoroughbred racehorses.	√	√	√			11(11)	√	√	No significant factors identified
Chan *et al.* (2000)	UK	PCs	Referral hospital (1) and university teaching hospital (1)	To evaluate the effectiveness of a technique that combined a modified open annular ligament desmotomy with passive open drainage as a primary surgical option for 12 horses with chronic digital septic tenosynovitis of more than 72 hours' duration.	√	√	√	√	√	12(12)	√	√	No significant factors identified
Cousty *et al.* (2017)	France	RXS	Referral hospital (1)	To evaluate the effects of arthroscopic lavage and repeated intra-articular administration of antibiotic on SF WCC and TP and % of neutrophils with septic arthritis and to evaluate if SF nucleated cells count, total protein, and % of neutrophils can serve as monitoring tools to predict the outcome.	√	√	√			62(35)	√		No significant factors identified

Crosby *et al.* (2019)	Australia	RXS	University teaching hospital (1)	To describe outcomes for horses and foals with synovial sepsis presented to a single hospital and to identify the factors associated with survival to discharge from hospital and with return to function.	√	√	√			186(161)	√	√	No. days of antimicrobial treatment, use of doxycycline.
Dabareiner *et al.* (2001)	USA	RCs	University teaching hospitals (2)	To determine clinical, radiographic, and scintigraphic abnormalities in and outcome of horses with septic or nonseptic osteitis of the axial border of the proximal sesamoid bones.	√	√	√	√	√	8(3)	√	√	No significant factors identified
Duggan and Mair (2019)	UK	RCo	Referral hospital (1)	To identify clinically significant variations in the outcome of horses treated for septic calcaneal bursitis using either a needle or bursoscopic lavage.	√	√	√			29(29)	√	√	No significant factors identified
Findley *et al.* (2014)	UK	RXS	Referral hospitals (4)	To report the clinical features, surgical treatment and outcome of horses presented for solar foot penetrations involving synovial contamination or sepsis and to identify factors associated with survival to discharge and return to athletic function.	√	√	√			95(95)	√	√	Increasing no. days to presentation, location of injury on frog sulcus, bone involvement, breed, hospital, no. surgeries

Fraser and Bladon (2004)	UK	RXS	Referral hospital (1)	To report the outcome of the tenoscopic treatment of injuries involving the DFTS.	√	√	√		√			39(39)	√	√	No significant factors identified
Frees *et al.* (2002)	USA	RCs	University teaching hospital (1)	To determine clinical findings, medical treatments, and outcomes of horses with open injuries to DFTS that had surgical treatment with tenoscopy	√	√	√	√	√			20(20)	√	√	No significant factors identified
Gamal *et al.* (2010)	Egypt	RXS	Working equid hospital (1)	To investigate factors that might influence the success of treatment for synovial sepsis in a charitable clinic.	√	√	√					57(10)	√		No significant factors identified
Gibson *et al.* (1989)	USA	RXS	University teaching hospital (1)	To evaluate how the duration of injury, the joint involved or the method of treatment may affect outcome in open joint injuries.	√	√	√	√	√			58(58)	√	√	No significant factors identified.
Gillbertie *et al.* (2018)	USA	RXS	University teaching hospital (1)	To determine the association between bacterial culture and antimicrobial susceptibility outcome in horses with septic synovial structures; and identify risk factors affecting short-term clinical outcome and survival to discharge in horses treated for synovial sepsis.							√	206(206)	√		Positive bacterial culture, type of bacteria and MDR phenotypes
Groom *et al.* (2000)	USA	RCs	University	To determine the successful outcome for	√	√	√		√	√		8(8)	√	√	No significant

			teaching hospital (1)	horses having PIPjt arthrodesis with internal fixation in a concurrent environment of septic arthritis.										factors identified.
Haltmayer *et al.* (2017)	Austria	POs	University teaching hospital (1)	To evaluate the course of plasma SAA over time in patients undergoing treatment for injuries penetrating synovial structures and to evaluate plasma SAA as a potential marker for treatment response.	√	√	√					19(19)	√		No significant factors identified.
Hawthorn *et al.* (2016)	UK	RCc	Referral hospital (1)	To report the incidence of sepsis following rigid endoscopic surgery of synovial structures as well as to investigate variables associated with post-operative synovial sepsis and the use of electrosurgery.							√	16(16)	√	√	No significant factors identified.
Herdan *et al.* (2012)	New Zealand	RCs	University teaching hospital (1)	To describe three cases of horses affected by synovial sepsis associated with MDR bacteria.	√	√	√	√				3(2)	√		No significant factors identified.
Holcombe *et al.* (1997)	USA	RCs	University teaching hospitals and	To describe use of antibiotic-impregnated PMMA in the management of horses with open fractures, bone infections, and joint injuries.	√	√	√		√	√		19(2)	√	√	No significant factors identified.

			referral hospital (3)											
Honnas *et al.* (1991)	USA	RXS	University teaching hospital (1)	To determine the clinical features of septic tenosynovitis and to determine survival and soundness of horses after medical or surgical management.	√	√	√	√			25(25)	√	√	No significant factors were identified.
Honnas *et al.* (1992)	USA	RCs	University teaching hospital (1)	To determine the clinical features of septic arthritis of the DIPjt and to determine survival and soundness after treatment.	√	√	√	√	√		12(12)	√	√	No significant factors identified.
Honnas *et al.* (1995)	USA	RCs	University teaching hospital (1)	To describe the results of using autogenous cancellous bone grafting as an ancillary technique in the treatment of 6 horses with septic navicular bursitis and osteomyelitis of the distal sesamoid that resulted from deep punctures of the hoof.	√	√	√			√	6(6)	√	√	No significant factors identified.
Isgren *et al.* (2020)	UK	RXS	Mixed referral centres (7)	To analyse outcome of contamination/sepsis of the calcaneal bursae following endoscopic treatment, to identify prognostic factors associated with	√	√	√				128(128)	√	√	Antimicrobials prior to referral and tendinous involvement

				survival and to describe the bacterial isolates involved in the synovial infections.										
Kelmer *et al.* (2012)	Israel	RXS	University teaching hospital (2)	To report the use of indwelling IV RLP, using the saphenous or cephalic vein, to treat horses for synovial injury of the distal aspect of the limb.	√	√	√		√	√		44(44)	√	√	No significant factors identified.
Kidd *et al.* (2007)	UK	RCo	Not specified	To evaluate the levels of MMPs for monitoring septic arthritis and its treatment in horses and to relate them and other disease factors to their prognosis and survival.	√	√	√					32(32)	√		No significant factors identified.
La pointe *et al.* (1992)	Canada	RXS	University teaching hospital (1)	To present synovial fluid values, bacterial species implicated, treatment, and performance outcome in clinical cases of Standardbred racehorses with post-injection septic arthritis.	√	√	√	√				15(15)	√	√	No significant factors identified.
Lescun *et al.* (2006)	Australia	RXS	Referral hospitals (2)	To review cases of septic synovitis treated with CIAI and to report the clinical findings, complications associated with this method of treatment, and outcome.	√	√	√		√	√		22(22)	√	√	No significant factors identified.
Lopes *et al.* (2006)	USA	RCo	University	To describe and compare the clinical	√	√	√					33(16)	√	√	No significant

			teaching hospital (1)	presentation and outcomes of horses presented for tenoscopy of septic and non-septic tenosynovitis.									factors identified.
Madison *et al.* (1995)	USA	RCs	University teaching hospital (1)	To describe the clinical findings, treatment and outcome of two horses with *Candida* arthritis.	√	√	√		√	2(2)	√	√	No significant factors identified.
Marsh *et al.* (2011)	USA	RCs	University teaching hospitals (2)	To report outcome after removal of a portion of the intrathecal component of the DDFT in horses with chronic septic tenosynovitis complicated by demonstrable sepsis of the DDFT, unresponsive to conventional therapy.	√	√	√		√	4(4)	√		No significant factors identified.
McNally *et al.* (2013)	USA	RCs	Referral hospital (1)	To describe an open palmar/plantar annular ligament transection, tenosyn- oviotomy, and tenotomy of the distal lateral branch of the superficial digital flexor tendon (SDFT) with passive drainage and second intention healing in horses with synovial sepsis of the DFTS and to document survival, complications,	√	√	√	√	√	9(9)	√	√	No significant factors identified.

				and long-term outcome.										
Meagher *et al.* (2003)	USA	RXS	University teaching hospital (1)	To determine clinical details and long-term outcome in horses suffering from synovial sepsis or contaminated synovial wounds in which a balloon constant rate infusion system was used for delivery of antimicrobials.	√	√	√	√	√	23(23)	√	√	No significant factors identified.
Meijer *et al.* (2000)	Netherlands	RXS	University teaching hospital (1)	To present the results obtained with the joint lavage technique in horses with septic arthritis under European conditions.	√	√				39(27)	√	√	No significant factors identified
Milner *et al.* (2014)	UK	RXS	University teaching hospital (1)	To investigate pre-, intra- and post-operative factors associated with short-term survival in a group of horses that underwent endoscopic treatment for synovial sepsis in a single hospital population.	√	√	√			214(214)	√		Pre- and post-operative TP on SF, presence of wound, number of surgical procedures, GA OOH.
Mostafa *et al.* (2014)	Egypt	RCs	University teaching hospital (1)	To record clinical, radiographic, ultrasonographic, arthroscopic and bacteriological findings in septic tarsitis in horses.	√	√	√	√		14(14)	√		No significant factors identified.
Olds *et al.* (2006)	USA	RCs	University	To determine the frequency of septic	√	√	√			682(7)	√	√	No significant

			teaching hospital (1)	arthritis developing after elective arthroscopy and to evaluate associations between various factors and development of post-operative septic arthritis.									factors identified.
Peremans et al. (2001)	Belgium	RCs	Not specified	To describe 34 cases of monoarticular arthritis in the horse with the results of treatment.	√	√	√			34(34)	√	√	No significant factors identified.
Pille *et al.* (2009)	Belgium	RXS	University teaching hospital (1)	To describe the clinical aspects and the outcome of synovial contamination and infection in a large group of horses and to determine possible prognostic factors.	√	√	√	√		195(160)	√	√	Cause of infection, presence of radiographic abnormalities, regional antibiotic perfusion, duration of clinical signs prior to treatment.
Post *et al.* (2003)	UK	RXS	University teaching hospitals (2)	To identify the specific features of the clinical presentation, diagnostic investigation and treatment of septic calcaneal bursitis associated with an open wound, and to determine their influence on prognosis.	√	√	√	√	√	24(24)	√	√	No significant factors identified.

Prendergast *et al.* (1999)	Ireland	RCs	University teaching hospital (1)	To review the clinical features of tenosynovitis of the digital sheath in ten affected horses and to record the outcome after medical and surgical management with and without the use of a rest shoe in the recovery period.	√	√	√			10(10)	√	√	No significant factors identified.
Ribera *et al.* (2014)	Spain	RCs	University teaching hospital (1)	To describe the positive clinical experience after injecting intra-synovial imipenem in three septic joints and one septic tendon sheath as the last treatment resort.	√	√	√		√	4(2)	√		No significant factors identified.
Rubio-Martinez *et al.* (2012)	Canada	RXS	University teaching hospital (1)	To describe the clinical use of RLP with antimicrobials and its complications and outcome in a large series of horses.	√	√	√		√	174(96)	√	√	Multiple synovial structures, systemic antimicrobials.
Schneider *et al.* (1992)	USA	RCs	University teaching hospital (1)	To report the results of horse with septic arthritis or tenosynovitis that were treated by draining the synovial space through an open incision and intra- articular or intra-thecal antibiotic injections.	√	√	√	√		26(26)	√	√	No significant factors identified.

Schneider *et al.* (1992)	USA	RXS	University teaching hospital (1)	To report the results of 192 horses with naturally occurring septic arthritis/tenosynovitis.	√	√	√	√		192(126)	√	√	No significant factors identified.
Smith *et al.* (2006)	UK	RXS	Referral hospital (1)	To investigate the likelihood that a horse treated for septic digital tenosynovitis will return to its previous level of athletic function.	√	√	√	√		90(90)	√	√	No significant factors identified.
Stewart *et al.* (2010)	USA	RXS	University teaching hospitals (2)	To present the technique for intra-articular Mila catheter placement and report the clinical outcomes of 38 cases of equine synovial trauma and/or infection treated with broad-spectrum antimicrobials administered via an ISC.	√	√	√	√	√	38(38)	√	√	No significant factors identified.
Stöckle *et al.* (2018)	Germany	RCo	Referral hospital (1)	To compare the development of post-surgical complications after elective, clean or orthopaedic surgical procedures in equines with and without perio-operative antibiotic treatment.	√	√	√			652(7)	√		No significant factors identified.
Suarez-Fuentes *et al.* (2018)	USA	RCs	University teaching	To report the outcome of horses undergoing navicular bursotomy for the treatment of	√	√	√	√	√	19(19)	√	√	No significant factors identified.

			hospital (1)	contaminated or septic navicular bursitis.										
Summerhayes (2000)	UK	RCs	Referral hospital (1)	To investigate the value of gentamicin-impregnated collagen sponges for the treatment of traumatically induced synovial sepsis.	√	√	√	√	√		8(8)	√	√	No significant factors identified.
Swinebroad *et al.* (2003)	USA	RCs	University teaching hospital (1)	To determine clinical, radiographic, and scintigraphic abnormalities in and treatment and outcome of horses with osteomyelitis of the proximal aspect of the radius	√	√	√				5(3)	√	√	No significant factors identified.
Taylor *et al.* (2010)	UK	RXS	Referral hospitals (2)	To investigate the influence of synovial fluid culture results on both the short- and long-term prognosis for horses treated for septic synovitis.	√	√	√				206(206)	√	√	No significant factors identified.
Vatistas *et al.* (1996)	USA	RCs	Multiple referral centres (>1)	To determine the signalment, clinical signs, and response to treatment of horses with infectious bicipital bursitis.	√	√	√	√		√	4(4)	√	√	No significant factors identified.
Walmsley *et al.* (2011)	Australia	RXS	University teaching hospital (1)	To determine the prognostic value of variables obtained at admission and during treatment for infection of a synovial structure.	√	√	√				75(75)	√	√	No significant factors identified

Wereszka *et al.* (2007)	USA	RXS	University teaching hospital (1)	To identify factors associated with outcome (survival and return to function) following treatment of horses with septic tenosynovitis.	√	√	√		51(51)	√	√	Duration of clinical signs, sepsis of adjacent joint, partial or complete tendon rupture, presence of pannus and tendon injury.
Wright *et al.* (1999)	UK	RXS	Referral hospital (1)	To report and describe endoscopic approach to the navicular bursa for treatment of contaminated and septic navicular bursa.	√	√	√		16(16)	√	√	No significant factors identified.
Wright *et al.* (2003)	UK	RXS	Referral hospital (1)	To describes a retrospective analysis of cases treated endoscopically with no adjunctive surgical interference and, whenever possible with primary wound closure.	√	√	√		140(121)	√	√	Bone pathology, surgical findings, breed of horse, a combination of synovial structure involvement and regional antimicrobials.

Abbreviations: CC=Case-control, CDET= common digital extensor tendon, CIAI = continuous intrasynovial antimicrobial infusion, Co=Cohort, DDFT = deep digital flexor tendon, DFTS=digital flexor tendon sheath, DIPjt= Distal interphalangeal joint ES=experimental study, GA= general anaesthesia,

IO=intraosseous, ISC=intra-synovial catheter, IV = intravenous, MDR=Multi-drug resistant, MMP= matrix metalloproteinases, OOH = Out of hours, PCo=Prospective cohort, PCs = Prospective case series, PIPjt – Proximal interphalangeal joint, PMMA=polymethylmethacrylate, POs = prospective observational study, RCo=Retrospective cohort study, RCS= Retrospective case series or case reports, RXS=Retrospective cross sectional study, RCc=Retrospective case control study, RLP=Regional limb perfusion, RTW = return to athletic function, SF= Synovial fluid, SSI = surgical site infection, STD= survival to discharge from hospital, Sx = surgery, TB – Thoroughbred, TC=*tuber calcanei*, TNCC= total nucleated cell count, TP= total protein, U/S = ultrasound, XS=Cross-sectional

†treatment techniques as defined in Table 1.

Appendix 2: *Details of descriptive case series identified during a scoping review investigating synovial sepsis.*

Synovial structure(s)	Author	Aim (Structure, Cause or Treatment)	Treatment details
Navicular bursa	Suarez-Fuentes *et al.* (2018)	Treatment – surgical technique	Navicular bursotomy
	Honnas *et al.* (1995)	Treatment – surgical technique	Use of autogenous cancellous bone graft
Distal interphalangeal joint	Honnas *et al.* (1992)	Describe cases and investigate outcome	Medical and surgical treatment with combinations of lavage, antimicrobials, drainage and arthrodesis of the DiPJt
Pastern	Bergstrom et al. (2020)	Describe cases and investigate outcome	Standard treatment and pastern arthrodesis.
	Groom *et al.* (2000)	Treatment – surgical technique	Lavage and arthrodesis of PIPjt with internal fixation and PMMA beads.
Digital flexor tendon sheath	Chan *et al.* (2000)	Treatment – surgical technique	Complete transection of the palmar/plantar annular ligament of the fetlock and proximal digital annular ligament, removal of fibrin, selective debridement and synovectomy, followed by lavage of the digital sheath.
	Frees *et al.* (2002)	Describe cases and investigate outcome	Tenoscopic lavage with lactated ringers and 10% DMSO, PMMA beads, drainage, systemic and regional antimicrobials.
	Marsh *et al.* (2011)	Treatment – surgical technique	Tenectomy of the intrathecal component of the DDFT, followed by stabilization in casts and subsequent corrective shoeing.
	McNally *et al.* (2013)	Treatment – surgical technique	Open drainage via tenosynoviotomy.
	Prendergast *et al.* (1999)	Treatment – surgical technique	Conservative and surgical management
Metacarpophalangeal/ metatarsophalangeal joint	Dabareiner *et al.* (2001)	Describe cases and investigate outcome – Osteitis of the	Arthroscopy or the MCPJt/MTPJt, surgical debridement of the axial border of the sesamoid bones with systemic and regional antimicrobials.

		axial border of the proximal sesamoid bones	
Common Digital Extensor tendon sheath	Booth et al. (2004)	Treatment - surgical technique	Resection of the affected tendon and ablation of the tendon sheath. Closure with either closed suction drain, penrose drain, passive open drainage or second intention healing.
Small tarsal joints	Booth et al. (2001)	Treatment – antimicrobial implant	Gentamicin-impregnated PMMA beads placed in 7-8mm drill tracts created across TMT with lavage and systemic antimicrobials. Ancillary treatments include removal of bone fragments and fourth metatarsal bone fracture treatment.
Tarsocrural joint	Mostafa *et al.* (2014)	Describe cases and investigate outcome	Arthroscopic lavage, systemic and regional antimicrobials
Elbow	Swinebroad *et al.* (2003)	Describe cases and investigate outcome	Lavage and systemic antimicrobials
Bicipital Bursa	Vatistas *et al.* (1996)	Describe cases and investigate outcome	Lavage, systemic and regional antimicrobials and drainage
General synovial structures	Ashton (2018)	Cause of infection - Blackthorn synovitis	Two-stage procedure using a perisynovial ultrasound guided electrosurgical dissection technique and then endoscopy.
	Butson *et al.* (1996)	Treatment – antimicrobial implant	Gentamicin-impregnated PMMA beads inserted into the synovial cavity.
	Byrne *et al.* (2020)	Cause of infection - Unknown origin of synovial sepsis	Lavage with systemic and regional antimicrobials.
	Herdan *et al.* (2012)	Cause of infection – MDR bacteria	Lavage with systemic and regional antimicrobials as well as specific extra treatments for different synovial structures.
	Holcombe *et al.* (1997)	Treatment – Antimicrobial implant	Use of antimicrobial impregnated PMMA beads
	Madison *et al.* (1995)	Cause of infection - *Candida spp.*	Lavage, antimicrobials and antifungals

	Meijer *et al.* (2000)	Describe cases and investigate outcome	Lavage and systemic antimicrobials
	Peremans *et al.* (1991)	Describe cases and investigate outcome	Lavage, systemic and regional antimicrobials
	Ribera *et al.* (2014)	Treatment – regional antimicrobials	Intra-synovial Imipenem after previous treatments of lavage, systemic and local antimicrobials
	Schneider *et al.* (1992)	Describe cases and investigate outcome	Lavage, systemic and regional antimicrobials and open drainage
	Summerhayes (2000)	Treatment – Antimicrobial implant	Gentamicin impregnanted collagen sponges

Abbreviations: CDET – Common digital extensor tendon, CIAI – continuous intrasynovial antimicrobial infusion, DDFT – deep digital flexor tendon, DiPjt – distal interphalangeal joint, DMSO - Dimethyl sulfoxide, MCPjt – metacarpophalangeal joint, MDR – multidrug resistance, MTPJt – metatarsophalangeal joint, PiPjt- Proximal interphalangeal joint, PMMA - polymethyl methacrylate, TMT – tarsometatarsal joint

Appendix 2: *Key findings of analytical observational studies from a scoping review investigating treatment outcomes after synovial sepsis*

Risk factor	Structure or type of injury if specified*	Author of studies (year)	Measures of association [Statistical test]
Horse factors	Calcaneal bursae	Duggan and Mair (2019)	A statistically significant difference was identified between age and survival to discharge (P = 0.043), with older horses having a reduced likelihood of survival to discharge. [Fishers Exact Test]
		Lescun et al. (2006)	Female sex (P = 0.05) associated with reduced likelihood of RTW. [Fishers Exact Test]
Injury		Lescun et al. (2006)	Wound or iatrogenic infection source (P = 0.05, OR 0.086, 95% CI 0.008-0.878) was associated with reduced likelihood of RTW. [Logistic regression models and Fishers Exact Test]
		Schneider et al. (1992)	The horses with infected tendon sheaths survived (n=14) and were released from the hospital, compared to horses with joints affected, and this difference was significant (P<0.05). [Statistics not specified]
Duration of clinical signs prior to referral	DFTS	Fraser and Bladon (2004)	Horse treated >36 hours from the time of injury are associated with reduced likelihood of RTW compared to horses treated <36 hours from time of injury (P=0.03) [Fishers Exact Test]
		Gibson et al. (1989)	Horses examined > 24 hours after the initial injury had a significantly higher change of developing septic arthritis (p<0.05), and thus were less likely to survive (p<0.0014) [Chi-squared and Fishers exact test]
		Pillie et al. (2009)	For horses with penetrating wounds or nail punctures, the duration of clinical signs prior to treatment was significantly shorter (p<0.01) in horses with a successful outcome (mean 4 days, SD 8) compared to non-successful cases (15 days, SD 12). [Logistic regression and ANOVA]
		Pillie et al. (2009)	For horses with penetrating wounds, the duration of clinical signs prior to treatment was significantly shorter in horses with a successful outcome (mean 4 days SD 8) compared to those with a non-successful outcome (mean 15 days, SD 12) (P<0.01) [Logistic regression and ANOVA]
Synovial fluid parameters		Kidd et al. (2007)	In the horses that survived, the ratio of proMMP9:proMMP2 was 3.01(SE – 0.58) compared with those euthanized 14.5 (SE-4.39) (P=0·0019) [Unpaired t test + Mann-Whitney test OR Welch's correction test]

		Kidd et al. (2007)	Mean WCC of the synovial fluid of horses that survived (53.7 x 10^9 cells/L) (SE – 20.1 x10^9/L) was significantly lower than that of the horses that were euthanized (83.2 x10^9 cells/L) (SE - 10.9x10^9/L) (P=0.022) [Unpaired t test + Mann-Whitney test OR Welch's correction test]
		Kidd et al. (2007)	The mean levels of proMMP9 was significantly lower in those horses that survived (2079, SE-331.6), than euthanized (3208 SE- 323.2) (P=0·0052) [Unpaired t test + Mann-Whitney test OR Welch's correction test]
Bacterial culture		Taylor et al. (2010)	Culture of a bacterial genus (not including S. aureus) resulted in reduced likelihood of survival compared to negative culture (OR 13.9, CI 2.76-69.93, P<0.001) [Fishers Exact Test]
		Taylor et al. (2010)	Culture of S. aureus reduced likelihood of survival and unable to return to its previous level of performance compared to horses with a negative culture (Survival - OR 29.5, CI 5.65–154.5, P<0.001) (RTW - P = 0.015; OR 6.38; CI 1.42–28.6) [Fishers Exact Test]
		Taylor et al. (2010)	Horses that have a positive culture were less likely to survive and RTW than horses with a negative culture (OR 0.42, CI 0.20–0.85, P=0.01) [Fishers Exact Test]
		Taylor et al. (2010)	Horses with a culture of Staphylococcus aureus from a synovial structure were less likely to RTW than horses with a negative culture (P = 0.015, OR 6.38, CI 1.42–28.6) [Fishers Exact Test]
		Taylor et al. (2010)	Horses with a positive bacterial culture from synovial fluid were significantly more likely to be subjected to euthanasia compared to a negative culture (OR 18.9, CI 4.15–86.13, P<0.001) [Fishers Exact Test]
		Walmsley et al. (2010)	Horses that have a positive culture are less likely to survive and return to athletic function than those horses with a negative culture (Survival P=0.016, RTW P=0.032) [Fishers exact test]
Tendon damage	DFTS	Fraser and Bladon (2004)	Some degree of tendon damage negatively affected RTW compared to no tendon damage (P=0.0116). [Fishers Exact Test]
Bone pathology	Calcaneal bursae	Duggan and Mair (2019)	Presence of bone damage of tuber calcaneus reduces likelihood of survival (P=0.024). [Fishers Exact Test]
		Kelmer et al. (2012)	Presence of osteomyelitis reduces likelihood of survival (P=0.01) and reduced likelihood of RTW (P=0.007) [Fishers Exact Test]
		Pillie et al. (2009)	The presence of radiographic abnormalities was significantly related (p<0.001) with the probability of unsuccessful outcome (survived without residual lameness). [Logistic regression and ANOVA]

	Calcaneal bursae	Post et al. (2003)	The presence of radiographic lysis of the tuber calcaneus was significantly associated with reduced survival (P<0.001) [Fishers exact test or Chi-Squared Test]
		Stewart et al. (2010)	Osseous involvement had a significant negative effect on lameness at discharge (P = 0.001) and on the long-term outcome (P = 0.02) [Wilcoxon or Kruskal-Wallis test].
		Walmsley et al. (2011)	The presence of bone pathology negatively affects survival and RTW compared to horses with no evidence of bone pathology (Survival P=0.004, RTW P=0.013) [Fishers exact test]
Number of surgical procedures	Calcaneal bursae	Post et al. (2003)	A significant difference was found between the number of cases that survived after a single surgical procedure (12/14; 86%) and multiple surgeries (1/7; 14%) (P<0.01) [Fishers exact test or Chi-Squared Test]
Regional antimicrobials		Lescun et al. (2006)	Total continuous intra-synovial antimicrobial infusion dose ≥ 3,000 mg of antimicrobial (P = 0.04, OR 0.351, 95% CI 0.124- 0.992) was associated with reduced likelihood of horses returning to their intended use. [Logistic regression models and Fishers Exact Test]
		Pillie et al. (2009)	The use of regional antibiotic perfusion was significantly related (p<0.05) with the probability of unsuccessful outcome (survived without residual lameness). [Logistic regression and ANOVA]
Plasma SAA post operatively		Haltmayer et al. (2017)	Horses with injuries older than 24 hr (that only needed one surgical intervention) had significantly lower median plasma SAA levels (P = 0.001) between 48 hr (median 776 mg/L) and 96 hr (median 202 mg/L) after surgery. [Wilcoxon test for paired samples]
Synovial fluid parameters post-operatively		Cousty et al. (2017)	At day 4 post arthroscopic lavage, the percentage of neutrophils within synovial fluid was lower in adult horses and foals with a favourable outcome than in adult horses and foals with an unfavourable outcome (p=0.03). [Mann-Whitney Test]
		Cousty et al. (2017)	The nucleated cell count was lower in adult horses and foals with a favourable outcome than in adult horses and foals with an unfavourable outcome at day 10, 12, and 14 (P = 0.001, 0.022, and 0.009, respectively). [Mann-Whitney Test]
	Synovial fluid parameters	Walmsley et al. (2011)	If horses had an unremarkable synovial fluid sample 4-6 days' post admission, those horses are more likely to RTW than those with evidence of synovitis or sepsis on their synovial fluid sample (P=0.044). [Fishers exact test]
Clinical findings at discharge	Working equids	Gamal et al. (2010)	Horses with severe lameness (9-10/10) at admission were 11.3 times more likely to be lame at discharge than those presenting with a 3–4/10 lameness (OR 11.3, Standard Error 9.42, p=0.04). [Fishers Exact Test and Univariable logistic regression]

	Stewart et al. (2010)	The degree of lameness at discharge was significantly associated the long-term outcome (P=0.0001) [Wilcoxon or Kruskal-Wallis test].

Abbreviations: ANOVA – analysis of variation, CI – confidence intervals, DFTS – digital flexor tendon sheath, Hr –hour, MMP – matrix metalloproteinases, OR – odds ratio, RTW – return to work, SAA – serum amyloid A, SD – standard deviation, SE – standard error, WCC – white cell count

CHAPTER THREE

Multicentre study investigating long term survival after surgical lavage of contaminated and septic synovial structures in horses

Abstract

Objective: To report the long-term survival of adult horses that were subjected to surgical lavage for treatment of contaminated and septic synovial structures.

Study Design: Multicentre, prospective observational trial.

Animals: Two hundred and forty horses presented for synovial sepsis at UK referral centres

Methods: Data for horses presented for treatment of synovial sepsis were collected over a 15-month recruitment period. Owners were contacted a minimum of 365 days after surgery to assess long term survival. Descriptive statistics, univariable and Cox proportional hazards models for post-operative survival time were developed.

Results: Survival to discharge was 228/240 (95%) and overall long term survival was 89.4% (185/207). Unknown cause of injury (p=0.017), increasing duration of surgery (p=0.003), increasing duration of antimicrobial treatment (p=0.003), increasing weight (p=0.008), forelimb injuries (p=0.027), and type of synovial structure (p=0.008) were found to be significantly associated with death using Cox proportional hazards models.

Conclusion: This study provides information on risk factors associated with survival and death after treatment for synovial sepsis at referral hospitals in the UK. Survival to discharge and long term survival was good. Heavier horses, injuries affecting the forelimbs, tendon sheaths and bursae were associated with poorer long term outcomes. In addition, longer duration of surgeries as well as increasing number of days of antimicrobial treatment were also found to be associated with a worse prognosis.

Clinical significance of impact: These findings help provide prognostic information for owners and veterinarians treating horses with synovial sepsis.

Introduction

Synovial sepsis or contamination is a potentially career ending and life threatening condition affecting horses (Richardson and Ahern, 2012, Wright et al., 2003). Treatment in the majority of cases involves aggressive and thorough lavage and appropriate antimicrobial therapy to eliminate the infection and restore a normal synovial environment (Milner et al., 2014, Richardson and Ahern, 2012, Wright et al., 2003). The presentation of conditions in adult horses somewhat differs from foals. In adult horses, the condition most commonly occurs due to a traumatic or penetrating injury to the synovial structure (Crosby et al., 2019, Milner et al., 2014, Wereszka et al., 2007, Wright et al., 2003) however, in foals, synovial sepsis most commonly occurs due to haematogenous spread often because of failure of passive transfer or secondary to another infection (Richardson and Ahern, 2012).

Survival after synovial sepsis varies between 44%-90% (Findley et al., 2014, Milner et al., 2014, Post et al., 2003, Wright et al., 2003) showing that despite appropriate treatment for this condition, there are still a significant number of cases that result in mortality. The identification of risk factors that influence this outcome is vital for providing veterinarians with evidence based guidelines to aid case management. Within the literature, only a small number of studies use multivariable analysis to investigate factors associated with short term and long term survival after treatment and the factors that have been identified are different between studies and lack consistency (de Souza et al., 2022). In addition, there are only a small number of studies that involve multiple centres (Findley et al., 2014, Isgren et al., 2020) or use prospective study design (Ashton, 2018).

Currently the evidence to guide clinical decision making is limited, and further research is needed to provide clarity on what factors are significantly associated with survival to improve outcomes. The objectives of this study were to report the long-term survival of adult horses that were subjected to surgical lavage for treatment of contaminated and septic synovial structures from multiple referral centres within the United Kingdom (UK). In addition, the aim of this study was to identify risk factors that were associated with the long-term survival of these horses.

Material and Methods

Case selection

A prospective, multi-centre study was performed to investigate survival after treatment for synovial sepsis. Ten equine referral hospitals within the UK were enrolled within the study based on their caseload, the presence of at least one Diplomate of the European College of Veterinary Surgeons and their willingness to contribute cases. Horses were included if they were presented for treatment of synovial sepsis to one of the enrolled hospitals during the recruitment phase (1st October 2019 to 1st January 2021) and were subjected to surgical lavage. Horses that were not subjected to any surgical treatment were excluded as were horses that were euthanised prior to or during the surgery. Surgical lavage was defined as any surgical procedure under standing sedation or general anaesthesia which involved either endoscopic lavage, an open approach or a through and through lavage for the treatment of a contaminated or septic synovial structure. The inclusion criteria for cases was kept as broad as possible to align the study to represent findings of horses presented for treatment in the UK. Horses greater than six months old were recruited. Cases of synovial sepsis or contamination included two or more of the following:

- Clinical findings: Horse with lameness localised to a synovial structure, synovial effusion, heat or pain on palpation
- Evidence of direct communication of a wound, a positive pressure distension test, or diagnostic imaging findings showing synovial contamination or foreign body penetration into a synovial structure
- Synoviocentesis parameters indicating inflammation with an elevated total nucleated cell count of greater than 10 x 10^9 cells/L, a total protein concentration greater than 20 g/L and polymorphonuclear cell count percentage greater than 75%.
- Horses with a positive bacterial culture from a synoviocentesis sample

Data collection

Data were captured using standardised collection forms that were initially tested in a small pilot study at one hospital prior to commencing the study (General Appendix 2). To investigate long term survival, a standardised telephone questionnaire was developed and owners and or referring vets were contacted following discharge from the hospital (General

appendix 4). The telephone questionnaire contained questions about ownership, current use of the horse, death including date of death or sale and cause if applicable. Questionnaires were conducted a minimum of 365 days after discharge from the hospital to investigate long-term outcome (Cook et al., 2010). All horses remained in the study until they died or were lost to follow-up. The telephone questionnaire follow up was conducted by the primary researcher (TDS) at nine hospitals, and by in house veterinarians at one hospital. Horses were lost to follow up if there was no response after at least three failed attempts to contact. The study design and protocol was reviewed and approved by the University of Nottingham ethics committee. Informed client consent was obtained for participation within the study and if not obtained the horse was excluded.

Statistical analysis

Variables were assessed and appropriate biological grouping was performed prior to further analysis. Descriptive statistics were calculated for all variables. Survival time was calculated from the date of admission to the date of death or censoring. Cases were censored if they were lost to follow-up or if the case was still alive at the end of the study period. If the horse was lost to follow up the date the horse's status was last known was used (the date of discharge from the hospital or otherwise). Kaplan Meier graphs were used to compare variables and explore the probability of survival. Univariable analysis was performed on all explanatory variables to identify any variables associated with survival to discharge. Those variables showing a moderate association ($p<0.2$) were then included within multivariable analysis. Correlations between continuous variables were assessed using Pearson correlation coefficients and if >0.8 then the most biologically plausible variable was chosen. Correlations between categorical variables were explored using Cramer 'V' statistical calculations. Variables with > 25% missing values were excluded from further analysis. A forwards stepwise elimination procedure was used to create Cox proportional hazards multivariable models. Variables were assessed with a likelihood ratio statistic and remained in the multivariable model if they significantly improved the fit of the model ($p<0.05$). Models were created around different points within the clinical presentation and decision making during a case. These time points created the following models; pre-operative and intra-

operative (model 1); and pre-operative, intra-operative and post-operative models (model 2). All variables were then forced back into the model, including those with missing data >20%, and model fit assessed based on likelihood ratio statistics. Cox proportional hazards assumptions were assessed graphically with Schoenfield residuals. Delta-beta values were calculated and any cases contributing to large delta-beta values (<0.4 or >0.4) were excluded and the model was then re-analysed. Interaction terms of biologically plausible associations were explored and any that were significant were included within the model and the model re-analysed. Statistical analysis was performed using SPSS (Version 28, IBM). Statistical significance was set at $p<0.05$.

Results

Two hundred and forty horses underwent surgical treatment at the referral hospitals during the recruitment period and recovered from surgery. Of the 240 horses, 104 were female (43.3%) and 136 were male (56.7%). The median age was 8 years old (range 1 – 26 years). There were 96 Thoroughbreds or Thoroughbred crosses, 20 Cobs, 86 Warmbloods (WB) or WB crosses, 18 Pony or Arabs, 14 Draft breeds and six Other breeds. Median weight was 513.5 (range 175 - 786kg). Two hundred and sixteen horses had one synovial structure affected, 21 had two structures, three horses had three structures affected. The most common synovial structure involved was the metacarpophalangeal or metatarsophalangeal joint (59 horses, 24.6%), followed by the digital flexor tendon sheath (42 horses, 17.5%) and the tarsocrural joint (29 horses, 12.1%). The forelimb was involved in 105 horses (43.8%) and the hindlimb was involved in 135 horses (56.3%).

The cause of injury was from a kick or trauma in 103 horses (42.9%), a thorn penetration in 37 horses (15.4%), a wire or other foreign body in 27 horses (11.3%), other causes in 20 horses (8.3%) and unknown in 53 horses (22.1%) of horses. The duration of injury prior to admission varied with 66 horses (66/240, 27.5%) presented within 12 hours of the injury occurring, 85 horses (85/240, 35.1%) presenting between 12-24 hours, 32 horses (32/240,13.3%) between 1-7 days, 35 horses (35/240, 14.6%) presenting more than seven days after the initial injury, and the duration not recorded in 22 horses (22/240, 9%).

Synoviocentesis on admission was performed in 173 horses (173/240, 72%). The median white cell count on admission was 63 x 10^9 cells/L (range 1 - 352 x 10^9 cells/L), median total protein concentration of 42 g/L (range 2 - 94g/L) and a median polymorphonuclear cell count 83% (range 23 - 100%). There were 91 horses that had a synovial fluid sample submitted for bacteriology, and of these 64/91 (70%) had a positive culture. The bacterial species cultured included Staphylococcus species (20 horses), Streptococcus species (21 horses), Coliform species (11 horses), and other species (12 horses). Of the horses presented, 170 horses had wounds (170/240, 70.1%). The median size of the wounds presented was three centimetres (range 1-20cm). When the depth of wound was reported, 13 were partial or superficial skin thickness, 102 were full skin thickness and 40 wounds had deeper tissues exposed. The surgical technique was minimally invasive endoscopy in 222 horses (222/240, 92.5%) and a method of through and through lavage with needles or open lavage in 18 horses 18/240, 7.5%), with 234 horses undergoing general anaesthesia (97.5%), and 6 horses having surgery under standing sedation (6/240, 2.5%). A median volume of 10 litres was used for lavage of the primary synovial structure (range 2-30 Litres). The median surgery time was 60 minutes (range 25 – 180 minutes) and median general anaesthesia time was 90 minutes (range 30 – 200 minutes).

During endoscopy, foreign material was identified in 49 horses (49/222, 22%). Osseous pathology that was related to the injury was identified in 43 horses (43/222, 19.4%). Cartilage pathology was present in 39 horses (39/222, 17.6%) and soft tissue pathology (involving injury to a ligament or tendon) was present in 51 horses (51/222, 23%). Pannus was present in 116 horses (116/222, 52.3%) and subjectively grouped as mild (n=63), moderate (n=30) and severe (n=33) respectively which was left to surgeon discrepancy. Synovial inflammation was graded depending on the presence of the following characteristics; hyperaemia, petechiation, proliferation and stunting of the synovial villi. These characteristics were grouped so that the presence of one characteristic related to mild inflammation, two or three related to moderate and if all four were present that equated to severe synovial inflammation. Synovial inflammation was present in 137 horses (137/222, 62%) and classified as mild

(n=69), moderate (n=45) and severe (n=23). Of the 170 horses that had wounds, 138 were resected (138/170, 81.1%), with 124 using sharp resection (with blade or other surgical instrument) (124/138, 90%), 14 horses had a combination of hydro-surgery and sharp resection (14/138, 10%). One hundred and thirty-six horses had details of wound closure (136/170, 80%), with 19 left partially or completely open to facilitate drainage. Four horses had active drains used and seven horses had penrose drains inserted. Intrasynovial antimicrobials were used in 223 horses, with the most common antimicrobial used being amikacin (n=207) and gentamicin (n=11) when specified. Antimicrobial implants were used in 16 horses, with three horses having an intra-synovial catheter placed and these were all used for treatment of septic calcaneal bursas. Two horses had polymethyl-methacrylate (PMMA) beads used intra-articularly, and 11 horses had collagen sponges used in an extra-synovial location within wounds. Two horses had both intra-synovial and extra-synovial antimicrobial implants used. Three horses had intraoperative intra-venous regional limb perfusion performed (IV-RLP).

Post-operatively, 130 horses had intra-synovial medication performed (130/240, 54%), and the most common antimicrobial was amikacin (118 horses), then gentamicin (9 horses). The dose of intra-synovial amikacin used was 100mg in 26 horses, 200mg in 17 horses, 300mg in 11 horses, 400mg in two horses, and 500mg in 55 horses. Intra-synovial medication was performed once in 29 horses, twice in nine horses, three times or greater in three horses. IV-RLP was performed in 66 horses post-operatively (66/240, 28%), most commonly using gentamicin (56 horses), amikacin (6 horses) and ceftiofur (2 horses). IV-RLP was performed once in 32 horses, twice in 25 horses, and three times of greater in eight horses. Horses were treated for a median of 10 days of antimicrobial treatment with a range of 1-36 days recorded. Most horses were treated with a combination of procaine penicillin and gentamicin (200 horses). Of the 228 horses that were discharged from the hospital, 162 (162/228, 71%) cases were discharged with antimicrobials with the most common antimicrobial being trimethoprim sulphonamides (97 horses), doxycycline (27 horses), enrofloxacin (28 horses) or another antimicrobial (7 horses). One hundred and twenty-four horses were discharged home with

analgesia, with the most common drug being phenylbutazone (119 horses) with a median of six days of treatment (range 2 – 15 days).

Of the 240 horses that recovered from the first surgical procedure, 228 horses (95%) survived to discharge from the hospital. All 12 horses that did not survive to discharge from the hospital were euthanised due to unresolved synovial sepsis. The median number of days of hospitalisation was seven days (range 1 and 36 days). Figure 1 shows the number of surgical procedures and the response of horses to treatment.

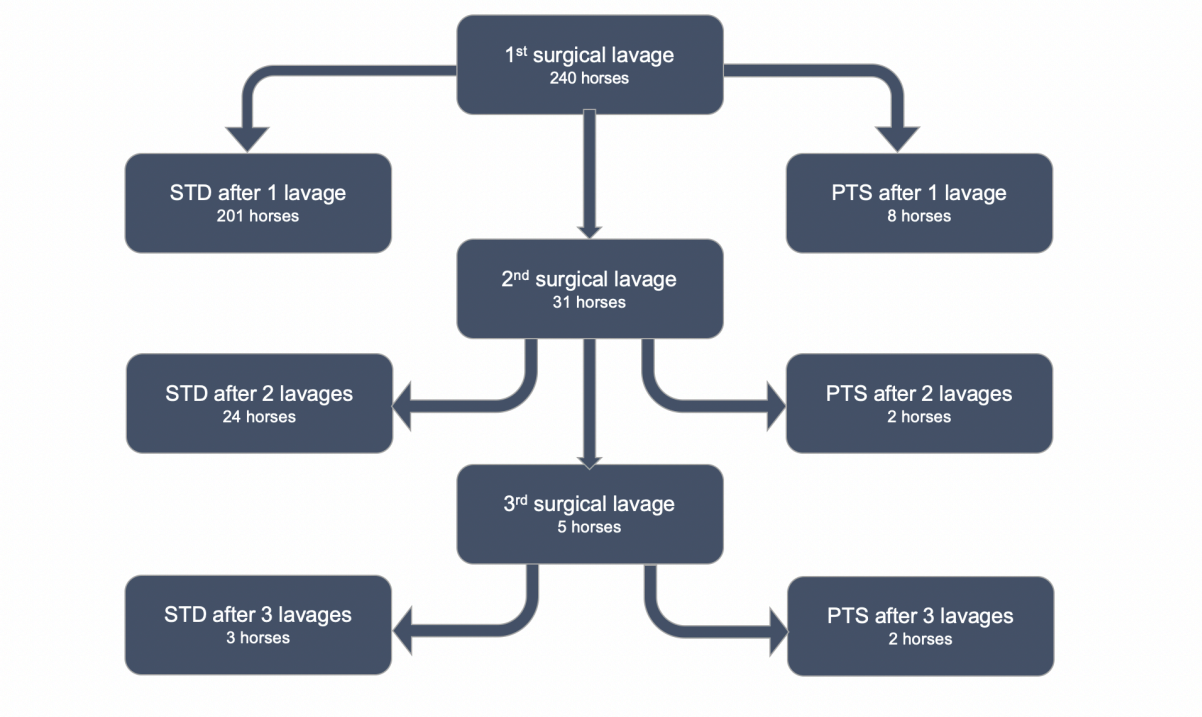

Figure 1: *Flow chart to show the movement of horses and the response to surgical treatment through to discharge from the hospital. (STD = survived to discharge, PTS –horses that were euthanised)*

When investigating long term survival, 33 horses were lost to follow up following hospital discharge (33/240,14%), leaving 207 horses available for analysis (207/240, 86%). The long-term survival of the horses in this study was 89.4% (185/207) at 365 days after surgery and 10.6% (22/207) were dead. Of the horses that died, 20 horses died due to reasons associated with synovial sepsis and two died for reasons other than synovial sepsis (broken

leg = 1, colic = 1). The median duration of follow up was 517.5 days (range 2 days and 917 days).

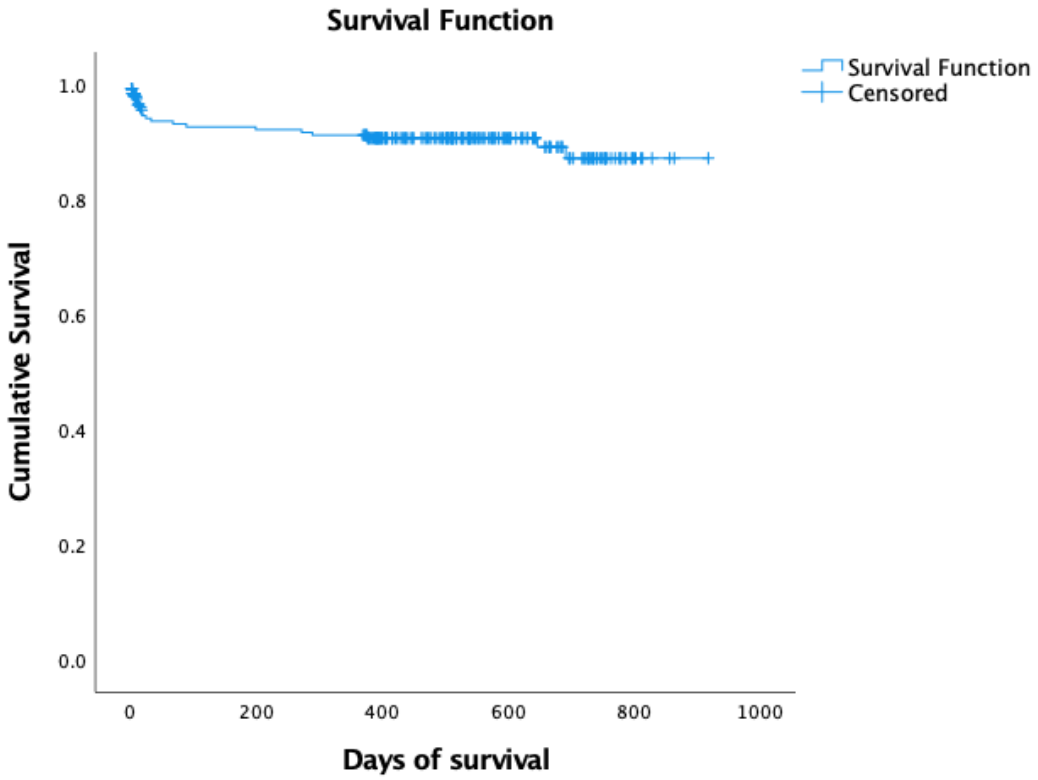

Figure 2: *Kaplan–Meier curves of the cumulative probability of survival after treatment for synovial sepsis.*

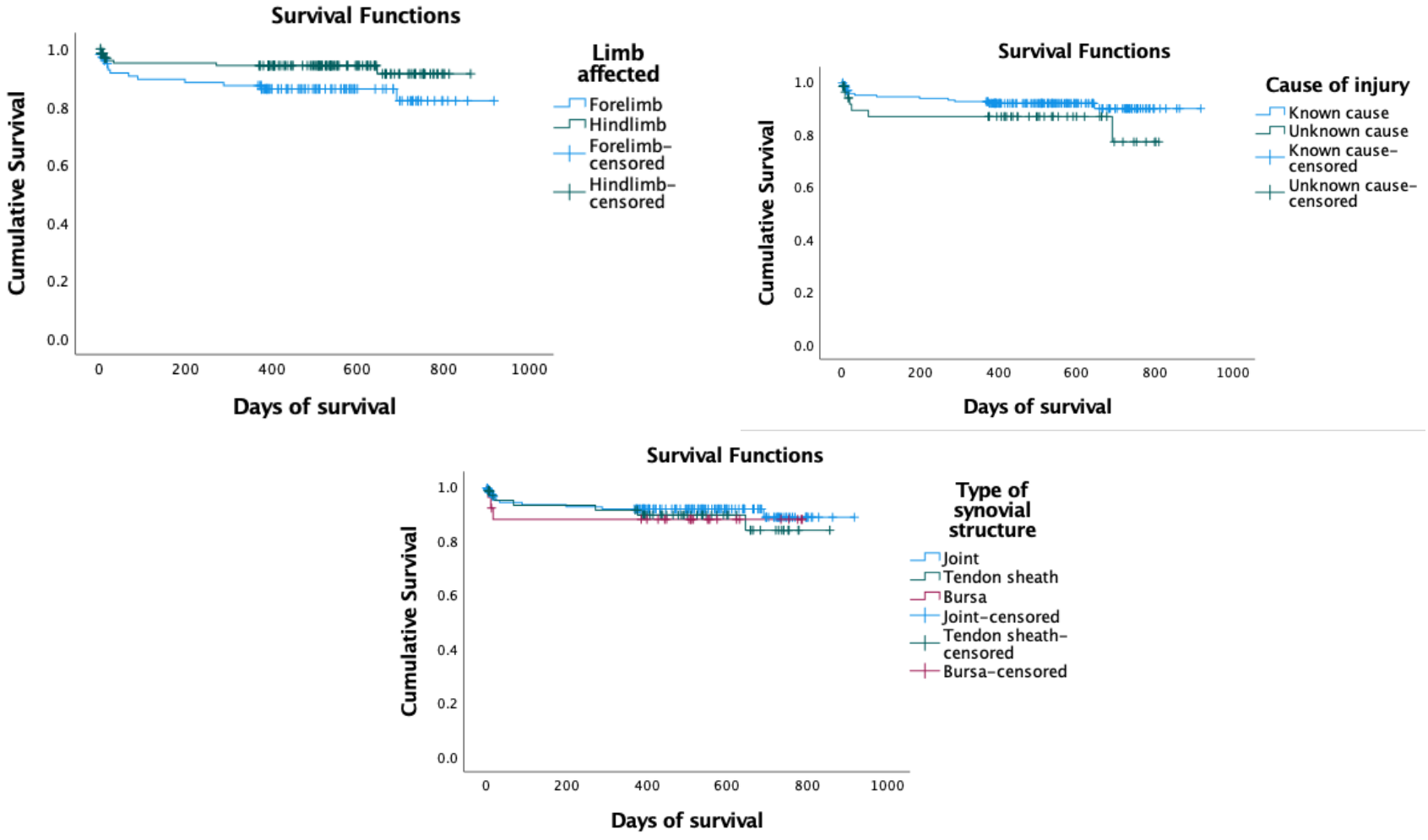

Figure 3*: Kaplan-Meier curves showing the comparison of survival times between horses in regards to different categorical variables (Forelimb or hindlimb, unknown or known cause of injury and type of synovial structure)*

The results of the univariable analysis of continuous and categorical variables associated with survival time are presented in Appendix 1 and 2. The results of the Cox proportional hazards models for factors associated with death following treatment for synovial sepsis are presented in Table 1. No significant associations were identified when pre-operative variables were considered on their own. When pre-operative and intra-operative variables (model 1) as well as pre-operative, intra-operative and post-operative variables (model 2) were assessed, this identified that cause of injury (known/unknown) and increasing duration of surgery were significantly associated with increased likelihood of death. When post-operative total protein concentration was forced back into the model (model 3) then increasing duration of antimicrobial treatment was re-introduced to be significantly associated with survival. When the type of synovial structure affected was forced back into the model (model 4) this identified that the limb affected (forelimb or hindlimb), increasing weight, cause of injury (known/unknown), increasing duration of surgery and the type of synovial structure (joint, tendon sheath or bursa) affected showed significant association with death. Figures 2 and 3 presents Kaplan-Meier graphs of the cumulative probability of survival for all horses that received surgical treatment for synovial sepsis and the distribution of cases in the significantly associated categorical variables.

Table 1: *Multivariable Cox proportional hazards models presenting risk factors associated with death in 240 horses presented for treatment of synovial sepsis at 10 referral hospitals.*

Variable		B	SE	Significance	Hazards Ratio	95.0% CI for Exp(B)	
						Lower	Upper
Model 1: Pre and intra-operative variables							
Cause	Known	Ref.					
	Unknown	1.665	0.725	0.022	5.288	1.277	21.905
Duration of Surgery	Minutes	0.029	0.010	0.003	1.029	1.010	1.049
Model 2: Pre, intra and post-operative variables							
Duration of surgery	Minutes	0.029	0.010	0.003	1.029	1.010	1.049
Cause	Known	Ref.					
	Unknown	1.758	0.735	0.017	5.802	1.375	24.483
Model 3: Post-operative TP and model 2							
Duration of antimicrobial treatment	Days	0.191	0.064	0.003	1.211	1.068	1.373
Model 4: Synovial structure and model 2							
Limb affected	Forelimb	Ref.					
	Hindlimb	-2.466	1.114	0.027	0.085	0.010	0.754
Weight	Kg	0.011	0.004	0.008	1.011	1.003	1.019
Cause	Known	Ref.					
	Unknown	2.240	0.846	0.008	9.391	1.790	49.264
Duration of Surgery	Minutes	0.058	0.017	<0.001	1.059	1.024	1.096
Type of synovial structure affected	Joint	Ref.		0.008			
	Tendon sheath	2.039	1.003	0.042	7.685	1.075	54.917
	Bursa	3.918	1.287	0.002	50.283	4.039	625.963

Abbreviations – TP total protein, Kg - kilogram

Discussion

This study provides information on risk factors associated with survival and death after treatment for synovial sepsis at referral hospitals in the UK. Long-term survival to one year after surgery was 89.4% and factors identified as significantly associated with death were unknown cause of injury, increasing duration of surgery, increasing number of days of antimicrobial treatment, increasing weight, limb affected (hindlimbs) and type of synovial structure (bursa and tendon sheaths).

For the outcome measured, it was chosen to investigate risk factors affecting long term survival rather than survival to discharge which has been used previously (Crosby et al., 2019, Findley et al., 2014, Milner et al., 2014). Long term survival was used because there is ambiguity around horses that are still lame and suffering from synovial sepsis that manage to make it to hospital discharge, and may be euthanized shortly afterwards. It was chosen to investigate long term survival to identify these cases and attempt to achieve a representation of the true survival rate.

Longer surgery times were associated with an increased likelihood of death. To demonstrate the results of model two, if a horse had a surgery duration of 90 minutes compared to 60 minutes, they had a 2.35 times greater risk of death. Surgery duration has been found to negatively affect outcome across several different procedures and species due to increased wound exposure, increased risk of surgical site infections, or anaesthesia related complications and others, however, it has not previously been identified as important in terms of outcomes after synovial sepsis (Verwilghen, 2019). Numerous factors could influence surgery duration including different hospital factors, surgeon experience, the synovial structure involved, the complexity of the procedure and the degree of injury (Richardson and Ahern, 2012). When these variables were assessed during the univariable analysis, no significant association with death was identified in this study and further investigation into surgery duration and any associated variables is warranted in the future.

Factors relating to the cause of injury have been identified to significantly affect outcome previously (de Souza et al., 2022, Findley et al., 2014, Milner et al., 2014). In this study, if the cause of injury was unknown to the owner or carer, this was associated with an increased likelihood of death (HR 5.802, 95%CI 1.375-24.483, p= 0.017). When considering cause of injury, other management factors were studied and it was found that there was no significant correlation between the duration of injury and admission or the presence of a wound and the cause of injury. The significance of the injury being unknown to the owner is not understood and further investigation is needed. In this study, detailed analysis and comparisons of the known causes of injury was not possible due to the small sample sizes. Within the literature, epidemiological studies investigating causes of synovial sepsis are limited to studies on iatrogenic injury (Smith et al., 2019, Steel et al., 2013). There has been some research into risk factors for traumatic injuries in horses previously (Owen et al 2012), and similarly, in a percentage of cases (19%), the cause of injury was unknown. Owen *et al* 2012 found that only a small number of traumatic injuries caused to synovial sepsis (1.3%). Further research on specific risk factors for injuries causing synovial sepsis could improve understanding and even help identify causes and reduce the frequency of synovial sepsis occurring.

Total protein concentration was initially excluded from model development as it had a large percentage of missing data (51.2%) as not all horses underwent synoviocentesis post-operatively, as this depended on hospital protocol and clinician preference. However, when forced back into the model, this revealed that an increasing duration of antimicrobial treatment was found to be significantly associated with an increased likelihood of death (HR= 1.211 95%CI 1.068 -1.373, p=0.003). This likely indicates that refractory cases received prolonged courses of antimicrobials. Importantly, this variable measured the number of days of treatment from the start of hospitalisation and including discharge medications, and did not include the number of days of antimicrobial treatment prior to hospitalisation, and so extrapolation before this point is discouraged. Previous studies have found conflicting results on how duration of antimicrobial treatment affects outcome. One such study found that increasing number of days of antimicrobial treatment resulted in an increased likelihood of death and reduced performance (duration of antimicrobial therapy > 12 days, OR 15.429,

95%CI 1.891–125.862, p= 0.011) (Wright, 2002). These results contrast with another study where they found that increasing number of days of systemic antimicrobial treatment had an increased likelihood of survival (OR1.11, 95%CI 1.04–1.17, p=0.004) (Crosby et al., 2019). The differences could be due to the modifications in the outcome measured, as in the present study and that of Wright *et al* 2003 the measured outcome was long term survival compared to survival to discharge used by others (Crosby et al., 2019, Wright et al., 2003). Furthermore, the differences in results could be due to the populations studied. The multicentre nature of this study compared to other studies based at one hospital means that nuances in specific hospital protocols may have influenced this variable. Interestingly, no significant difference was identified with survival between horses that were discharged with antimicrobials and those that were not, during univariable analysis.

When the type of synovial structure affected was forced back into the final model it remained significant as well as whether the forelimb or hindlimb was affected and increasing weight of the animal. Horses with injuries affecting hindlimbs were significantly less likely to die than horse with forelimbs affected. This has previously been identified as a significant risk factor (Rubio-Martínez et al., 2012) and interestingly, this only became significant when synovial structure was considered in the model. Previous authors have hypothesised that this is due to an increased proportion of the horse's weight being distributed through the forelimbs compared to the hindlimbs, so that if post-operative complications or lameness occurs it has a greater detrimental effect on the animal (Rubio-Martínez et al., 2012, Ross, 2011). Furthermore, in support of this view, heavier horses had an increased likelihood of death in this study. Different horse factors have previously been identified as significantly affecting outcome, but weight has not been reported (de Souza et al., 2022). Possible reasons for heavier horses having an increased likelihood of death could include the increased possibility of support limb laminitis, or the increased financial demands required for heavier horses (drugs and treatments). The type of synovial structure affected was categorised into broad groups including tendon sheaths, bursae and joints due to the small numbers of cases within each specific synovial structure preventing more detailed analysis. It was found that injuries involving tendon sheaths and bursae were significantly associated with death compared to

joints. Although this result has not been previously identified, the type of synovial structure has been shown to influence outcomes with earlier studies either incorporating it into multivariable analysis or specifically investigating different synovial structures (Crosby et al., 2019, Isgren et al., 2020, Wereszka et al., 2007). Further studies investigating specific synovial structures with larger sample sizes or comparing outcomes could be useful in clarifying this variable further.

The duration of time between injury and admission or treatment has been previously identified by two studies to be associated with poorer outcomes (Findley et al., 2014, Wereszka et al., 2007), however, in the present study this was found to have no association with long term survival consistent with other research (Isgren et al., 2020, Milner et al., 2014). The reason for these differences is unknown but may be because there are multiple factors that could affect the duration of time between the injury occurring and treatment being initiated. Examples of these contributing factors include the early identification of an injury, the availability of transport to a hospital, financial considerations, and initiation of medication prior to admission. Due to the relatively small numbers of cases within these groups means these cannot be full explored within this study. Future research is needed, including meta-analysis between studies, before firm conclusions can be made on how duration between injury and treatment affects outcomes following synovial sepsis. There was no significant association between surgeries performed out of hours compared to surgeries performed within working hours as previously found (Milner et al., 2014). This difference may be because the research in the present study was conducted at multiple hospitals compared to at a single centre (Milner et al., 2014) which may mean specific hospital factors are less influential on this variable.

Moderate or severe bone or soft tissue involvement, has previously been identified to be associated with death in relation to certain synovial structures such as calcaneal bursae or navicular bursae (Findley et al., 2014, Isgren et al., 2020). No significant association with long term survival was identified in this study and this may be due to the relatively small numbers of horses identified in these groups. In addition, the lack of significant association with survival could be because bone or tendon pathology does not affect whether the horse

remains alive in the long term, but could affect the horses return to soundness and therefore return to athletic function. Further investigation into long term return to athletic function could further clarify this. Horses that had more than one surgical procedure were found to be associated with increased likelihood of death during univariable analysis, however, this did not remain in the final multivariable model within this study. Previously, Milner *et al.* 2014 found increasing numbers of surgical procedures to be associated with death. This difference could be due to the relatively small numbers of horses having repeat lavage or differences in outcome variables investigated with survival to discharge measured before compared to long term survival used in this study. In addition, it could be due to different constructions of multivariable models with all variables being considered in the final model within this study compared to just post-operative variables in isolation being considered previously (Milner et al., 2014).

As with many studies, low case numbers and missing data were issues that were encountered. The use of multiple centres from around the UK did improve case numbers, however, case recruitment occurred during the COVID-19 pandemic and this could have influenced the number and distribution of cases presented, owners decisions, and the hospital's management of cases. Selection bias could have also influenced the results presented in this study. Horses that were presented to referral hospitals but not subjected to treatment were not included. The decision to euthanize a horse is based on numerous factors including financial and emotional decisions. Therefore, it was elected to exclude these horses and just investigate those that had the opportunity for treatment. Contact with the owner was attempted three times, and if no response, the case was censored with 14% of horses lost to follow up within this study, which is less than 20% which is generally classed as acceptable (Dettori, 2011).

The long-term survival rate reported in this study (89.4%) was similar to that reported in previous studies (Isgren et al., 2020, Wereszka et al., 2007, Wright et al., 2003) and the multicentre nature of the results should make them applicable to the UK population. Several risk factors associated with a poor outcome have been identified such as increasing surgery

duration, increasing weight, increasing number of days of antimicrobial therapy and injuries affecting forelimbs, bursae and tendon sheaths. It is hoped the results from this study will provide more evidence to aid case management for clinicians and owners and improve welfare of horses suffering from synovial sepsis.

APPENDIX TO CHAPTER THREE

Appendix 1: *Univariable associations of continuous variables with death after treatment for synovial sepsis*

Variable		B	SE	Significance	Hazards Ratio	95.0% CI for Exp(B)		% missing cases
						Lower	Upper	
Pre-operative data								
Age of horse	Years	0.014	0.041	0.736	1.014	0.936	1.099	5%
Weight of horse at admission	Kg	0.004	0.003	0.183	1.004	0.998	1.009	12.50%
White cell count at admission	$x10^9$ cells/L	0.003	0.002	0.165	1.003	0.999	1.007	21.30%
Total protein at admission	g/L	-0.01	0.013	0.453	0.99	0.965	1.016	29.60%
PMN admission	%	0.009	0.024	0.713	1.009	0.962	1.058	65.80%
Size of wound (max. diameter)	Centimetres	-0.016	0.08	0.844	0.984	0.841	1.152	51.70%
Intra-operative data								
Volume of lavage fluid for primary structure	Litre	0.105	0.038	0.006	1.111	1.031	1.197	6.70%
Time between admission and anaesthetic induction	Hours	-0.047	0.034	0.175	0.955	0.892	1.021	4.20%
General anaesthesia time (if performed)	Minutes	0.022	0.006	<.001	1.022	1.01	1.034	17.10%
Surgery time	Minutes	0.021	0.006	<.001	1.021	1.009	1.034	21.10%
Post-operative data								
White cell count post-operative	X 10^9 cells/L	0.024	0.008	0.002	1.024	1.009	1.04	46.70%
Total protein concentration post-operative	g/L	0.035	0.018	0.046	1.036	1.001	1.073	51.20%
Total number of days of antimicrobial treatment	Days	0.065	0.035	0.063	1.068	0.996	1.144	15.40%
Number of days of hospitalisations	Days	0.041	0.033	0.207	1.042	0.977	1.111	13.80%

Appendix 2: *Univariable associations of categorical variables with death after treatment for synovial sepsis*

Variable		B	SE	Significance	Hazards Ratio	95.0% CI for Exp(B)		Number of cases	%missing data
Preoperative data						**Lower**	**Upper**		
Practice	Practice 1	Ref.		0.962				37	0%
	Practice 2	0.079	0.674	0.907	1.082	0.289	4.058	30	
	Practice 3	-0.547	0.673	0.417	0.579	0.155	2.164	51	
	Practice 4	-0.223	0.839	0.79	0.8	0.155	4.144	19	
	Practice 5	-1.56	1.096	0.155	0.21	0.025	1.8	35	
	Practice 6	-0.136	1.096	0.901	0.873	0.102	7.476	8	
	Practice 7	-13.525	623.359	0.983	0	0	.	13	
	Practice 8	-0.517	1.096	0.637	0.597	0.07	5.115	12	
	Practice 9	-0.616	1.097	0.575	0.54	0.063	4.64	12	
	Practice 10	-0.149	0.73	0.838	0.862	0.206	3.606	23	
Breed	TB/TBx	Ref.		0.771				96	0%
	WB/WBx	-0.098	0.548	0.859	0.907	0.31	2.656	58	
	Other	-0.353	0.493	0.474	0.703	0.267	1.847	86	
Gender	Female	Ref.						104	0%
	Male	0.794	0.479	0.097	2.213	0.865	5.661	136	
Primary limb	LF			0.288				60	0%
	RF	-0.108	0.541	0.842	0.898	0.311	2.59	46	
	LH	-1.201	0.677	0.076	0.301	0.08	1.134	72	
	RH	-0.583	0.57	0.307	0.558	0.183	1.708	62	
Forelimb or Hindlimb	FL	Ref.						105	0%
	HL	-0.82	0.443	0.064	0.44	0.185	1.05	135	

Type of synovial structure	Joint	Ref.		0.747				153	0%
	Tendon sheath	0.309	0.476	0.516	1.362	0.536	3.461	62	
	Bursa	0.363	0.646	0.573	1.438	0.406	5.098	25	
Cause of injury	Known cause							187	0%
	Unknown cause	0.6	0.458	0.19	1.822	0.743	4.471	53	
Presence of wound	No							70	0%
	Yes	-0.161	0.458	0.724	0.851	0.347	2.087	170	
Depth of wound	Superficial or partial thickness			0.62				23	20.50%
	Deep/Full skin thickness	0.657	1.041	0.528	1.929	0.251	14.837	142	
	No wound	1.086	1.155	0.347	2.961	0.308	28.474	25	
Degree of wound contamination	None			0.315				8	45.80%
	Mild	-0.65	1.225	0.596	0.522	0.047	5.757	31	
	Moderate	-0.785	1.155	0.496	0.456	0.047	4.383	53	
	Severe	0.644	1.118	0.565	1.905	0.213	17.051	18	
	No wound	0.36	1.155	0.755	1.433	0.149	13.792	20	
Number of synovial structures affected	1							216	0%
	>1	0.692	0.553	0.211	1.997	0.676	5.903	24	
Duration of injury prior to admission	<12			0.706				66	0%
	12-24 hours	-0.063	0.607	0.917	0.939	0.286	3.086	85	
	Between 1 and 7 days	0.253	0.732	0.73	1.287	0.307	5.402	32	

	> 7 days	0.66	0.635	0.299	1.934	0.557	6.714	35	
	Unknown	0.628	0.731	0.39	1.874	0.447	7.86	22	
Were NSAIDs given prior to admission?	No							76	12.50%
	Yes	0.322	0.533	0.546	1.379	0.485	3.923	134	
Were systemic antimicrobials given prior to admission?	No							87	11.30%
	Yes	-0.152	0.475	0.749	0.859	0.339	2.178	126	
Was a combination of penicillin and gentamicin given prior to admission?	Pen/Gent given			0.909				80	12.10%
	Pen/Gent not given	-0.019	0.647	0.977	0.981	0.276	3.488	47	
	No Antimicrobial	0.2	0.54	0.711	1.221	0.424	3.522	84	
Intra-synovial antimicrobials given prior to admission	No							196	4.20%
	Yes	0.025	0.625	0.968	1.026	0.301	3.49	34	
NSAIDS used after admission	No							67	0%
	Yes	1.431	0.742	0.054	4.184	0.978	17.905	173	
Intra-synovial antimicrobials given after admission	No							105	4.60%
	Yes	-0.213	0.427	0.618	0.808	0.35	1.865	124	

Lameness on admission	Mild/no lameness	Ref.						59	25%
	Moderate/severe lameness	0.37	0.516	0.474	1.447	0.526	3.983	121	
Intra-operative									
Anaesthetic induction within working hours (between 9am-5pm)	Yes							186	0%
	No	0.76	0.443	0.087	2.138	0.897	5.099	54	
Type of surgical lavage technique	Endoscopy							222	0%
	Through and through lavage	-3.126	3.527	0.375	0.044	0.001	44.07	18	
Standing or General anaesthesia	GA							234	0%
	Standing	-3.04	6.103	0.618	0.048	0.001	7490	6	
Volume of lavage fluid categorised (litres)	5	Ref.		0.117				23	7.50%
	10	-0.232	1.12	0.836	0.793	0.088	7.114	100	
	15	0.614	1.121	0.584	1.848	0.206	16.619	42	
	>/=20	1.162	1.057	0.271	3.197	0.403	25.356	57	
Drainage of synovial structure (either wound or portals that communicated with synovial structure left open, penrose	No drainage performed	Ref.						31	4.60%

drain into synovial structure, intra-synovial cathether, active suction drain)	Drainage performed	0.387	0.557	0.487	1.472	0.494	4.386	198	
Were intra-synovial antimicrobials used?	Used	Ref.						223	2.90%
	Not used	0.25	1.027	0.808	1.284	0.171	9.616	10	
Presence of foreign material within the synovial structure	No	Ref.						156	4.60%
	Yes	0.191	0.527	0.717	1.21	0.431	3.396	49	
If a wound was present, was it closed?	No	Ref.		0.363				19	6.30%
	Yes	-0.9	0.668	0.178	0.406	0.11	1.506	136	
	No Wound	-0.457	0.692	0.509	0.633	0.163	2.456	70	
If a wound was present, was it resected?	No	Ref.		0.624				17	6.30%
	Yes	-0.622	0.775	0.422	0.537	0.117	2.454	138	
	No wound	-0.258	0.803	0.747	0.772	0.16	3.724	70	
Degree of Pannus present	Mild/none	Ref.						130	19.60%
	Moderate/severe	0.559	0.475	0.239	1.748	0.689	4.435	63	
Degree of synovial	Mild/none	Ref.						122	21.30%

inflammation present	Moderate/severe	0.382	0.465	0.411	1.465	0.589	3.645	67	
Soft tissue pathology present related to the injury (pre-operative imaging and intra-operative findings)	No	Ref.						133	23.30%
	Yes	0.392	0.51	0.443	1.479	0.544	4.021	51	
Osseous pathology present related to the injury (pre-operative imaging and intra-operative findings)	No	Ref.						180	7.10%
	Yes	0.048	0.556	0.931	1.049	0.353	3.12	43	
Articular cartilage pathology present related to the injury (pre-operative imaging and intra-operative findings)	No							151	20.80%
	Yes	-0.533	0.753	0.479	0.587	0.134	2.567	39	
Post-operative									
Number of changes of systemic	1 antimicrobial (or combination) during	Ref.		0.593				62	1.30%

antimicrobials during hospitalisation including the change to any discharge medications	hospitalisation - no changes								
	2 antimicrobials (or combinations of antimicrobials)- 1 change	-0.146	0.527	0.782	0.864	0.308	2.427	150	
	3 antimicrobials (or combinations of antimicrobials) – 2 ore more changes	0.439	0.673	0.514	1.551	0.415	5.796	25	
Was enrofloxacin given during hospitalisation or for discharge?	No	Ref.						174	13.80%
	Yes	0.727	0.479	0.13	2.068	0.808	5.29	33	
Was ceftiofur given during hospitalisation or for discharge?	No	Ref.						191	13.80%
	Yes	1.079	0.554	0.052	2.942	0.993	8.772	16	
Was doxycycline given during hospitalisation or for discharge?	No	Ref.						160	13.80%
	Yes	-0.371	0.554	0.503	0.69	0.233	2.045	47	

Was IVRP used post-operatively?	No	Ref.						158	6.70%
	Yes	0.103	0.464	0.825	1.108	0.446	2.75	66	
Number of IVRP treatments	1	Ref.						34	72.90%
	>1	-0.733	0.874	0.402	0.481	0.087	2.667	31	
Were intra-synovial antimicrobials used post-operatively?	No	Ref.						94	6.70%
	Yes	0.128	0.45	0.776	1.137	0.47	2.746	130	
Number of intra-synovial treatments performed	1	Ref.						89	45.80%
	>1	0.703	0.558	0.207	2.02	0.677	6.025	41	
Positive microbiological culture from synovial fluid taken either pre-operatively or intra-operatively	No	Ref.						23	67.50%
	Yes	1.762	1.038	0.09	5.823	0.761	44.528	55	
Number of surgical procedures	1	Ref.						209	0%
	>1	1.183	0.458	0.01	3.263	1.329	8.012	31	
Was synoviocentesis	No	Ref.						90	5%

performed post-operatively?	Yes	0.11	0.444	0.805	1.116	0.467	2.665	138	
Number of synoviocentesis samples taken	1	Ref.						56	42.50%
	>1	-0.056	0.54	0.918	0.946	0.328	2.727	82	

Abbreviations: GA – general anaesthesia, GP – general purpose, IVRP- intravenous region limb perfusion, LF – left fore, LH –left hind, NSAID – non-steroidal anti-inflammatory, RF – right fore, RH – right hind, TB – thoroughbred, WB – warmblood.

CHAPTER FOUR

Concluding discussion

Introduction

The studies within this thesis provide important evidence based research to influence decision making and improve outcomes after synovial sepsis. Chapter two has identified key features of the studies within the previous literature on synovial sepsis and the reported risk factors affecting treatment success. Chapter three has described the survival data on horses being treated for synovial sepsis using a multi-centre prospective study and has reported several important risk factors associated with poor outcomes.

Scoping review

The study in Chapter two presents the first structured, objective literature review investigating synovial sepsis. Only a small number of scoping reviews have been performed within the veterinary literature, but they are gaining rapid interest in human medicine as an evidence synthesis tool (Curtis et al., 2019, de Souza et al., 2022, Grant and Booth, 2009, Munn et al., 2018b). A scoping review was chosen because of the specific features and advantages it has compared to other reviews (Grant and Booth, 2009). These include the ability to map and categorise studies, identify themes, investigate research conduct and provide a broad overview of what we know so far (Munn et al., 2018a, Munn et al., 2018b). One other possible aim of a scoping review is to assess the feasibility of performing a systematic review. Systematic reviews and meta-analysis sit at the top of the evidence synthesis pyramid and aim to answer a specific question in regards to a treatment or outcome and include an assessment of bias (Munn et al., 2018a, Jeremy Howick, 2009 and 2011). However, to perform a systematic review, the literature must possess certain similar qualities, for example, the population examined, the outcome measured and the use of appropriate statistical analysis (Grant and Booth, 2009, Munn et al., 2018a). In addition, there needs to be enough of these similar studies to be able to draw appropriate conclusions. It was the authors impression, that there was wide variation in the studies investigating synovial sepsis, and hence a scoping review was chosen.

Research conduct

The findings from the scoping review are broadly split into those relating to research conduct, and those relating to risk factors affecting outcome. The key findings of research conduct included the relatively small number of studies that investigate synovial sepsis. Only 61 studies out of 1071 studies investigated outcome, with a range of study designs used. Themes of the 61 studies included the small numbers of cases and that most were based at single hospital. In addition, many were retrospective studies using hospital records for data collection. If it was an observational study, many studies did not account for the multifactorial associations that could contribute to outcomes with only eight studies using appropriate statistical techniques with multivariable analysis. The outcomes measured were also different between studies with lack of consistency in reported time frames. A main feature of the research conduct of the studies was the variation in inclusion criteria for a case of synovial sepsis or contamination. There were differences in the number of criteria specified, in the synovial parameter ranges, and differences in the separation of contaminated synovial structures or those with established infection. Similar issues in a standardised definition of septic arthritis occur within the human literature. Many studies use 'Newman's criteria' as gold standard (Newman, 1976) however others use different recommendations (Turner et al., 2021). Newman's criteria present an interesting concept that recommends cases to be categorised dependent on the progression of disease, but still allows them to be classified under an umbrella term as septic arthritis. It suggests different groups of septic arthritis where either an organism was isolated from the joint, an organism was isolated from elsewhere (i.e. blood culture), or where no organism was isolated but there was histological or radiological evidence of infection or where turbid synovial fluid was aspirated (Newman, 1976). In Chapter one, the limitations of the current diagnostic techniques we use in equine hospitals were discussed. The gold standard of diagnosis is considered as the positive culture of a microorganism from synovial fluid (Richardson and Ahern, 2012). This takes approximately 48 hours to yield a result, and it is not practical in a clinical setting, leading to welfare issues if treatment is delayed till this time. In addition, the low yield of positive results could lead to misdiagnosis. There is a lack of a readily available accessible, rapid, sensitive and specific test for the diagnosis of synovial sepsis. Development of this test would be a significant breakthrough in early and clear diagnosis of cases needing treatment. In addition, one of the

main recommendations from the scoping review was the development of a consensus statement to provide guidelines and agreement for the diagnosis of synovial sepsis considering all the limitations in the current methods of diagnosis. There are numerous statements available within the veterinary literature (ECEIM, 2021) and a common agreement could provide clarity between studied populations.

Survival results

The survival rate at 365 days after surgery for synovial sepsis was 89.4%. Factors significantly associated with death were increasing duration of surgery, an unknown cause of injury, the type of synovial structure affected, forelimbs, increasing weight and increasing duration of antimicrobial treatment. Forelimb injuries were significantly associated with death compared to injuries affecting the hindlimbs. The latter risk factor has been found previously to be significant when looking at outcomes after synovial sepsis and has been suggested to be due to horses distributing more weight through their forelimbs (Ross, 2011, Rubio-Martínez et al., 2012). In support of this view, heavier horses had an increased likelihood of death. Interestingly, no significant breed association was identified. If horses are heavier or overweight for their height and breed, this could lead to a relative increase in forces distributed through their limbs, and exacerbate any post-operative complications or recovery. In human medicine, obesity is a risk factor negatively associated with survival and can significantly affect recovery and progression of orthopaedic disease (Abdelaal et al., 2017, Parratte et al., 2014). In horses, both anaesthetic related complications and post-operative complications associated with increasing weight are becoming more widely recognised (Hill et al., 2020, Laurenza et al., 2020, Johnson et al., 2009). Neither body condition scoring nor body mass index calculations were performed in this study, and this presents an area for further research and clarification.

From the scoping review, it had been noted that features of systemic antimicrobial use have been present within previous literature, but the results have been conflicting (Crosby et al., 2019, de Souza et al., 2022, Rubio-Martínez et al., 2012, Wright et al., 2003). Within this study, a longer duration of antimicrobial treatment was significantly associated with increased likelihood of death. This may be because cases that have not responded to initial therapy are

commonly treated with repeat lavage, longer courses of antimicrobials as well as prolonged hospitalisation. In this study, themes of treatment were evident between hospitals, for example, 67.5% of horses were discharged from the hospital with antimicrobials, with some hospitals discharging horses with oral trimethoprim sulphonamides as routine, whereas others administering no medications. Interestingly, no significant difference in death was found between horses discharged home with antimicrobials and those that were not which raises a question about the decision making behind prolonged courses of antimicrobials. The decision to stop antimicrobial therapy post-operatively is often subjective and clinician driven, and there is currently no reported evidence guiding these decisions. One study has provided justification for decision making in their study advising that “administration continued until there was consistent improvement in lameness, and reduced surface temperature adjacent to the affected cavity, synovial distension, perisynovial swelling and engorgement of visible draining veins” (Wright et al., 2003). With increasing antimicrobial resistance and pressure on the veterinary industry to reduce inappropriate antimicrobial use, further research on duration of antimicrobial treatment would be useful in guiding clinicians. This was not investigated further in this study, and this research would ideally be a randomised controlled trial to be able to draw useful conclusions.

Increasing duration of surgery was also found to be a significantly associated with death. This has not previously been identified as a factor affecting outcomes after synovial sepsis, but surgery duration has been found to be associated with non-fatal and fatal complications associated with anaesthesia (Laurenza et al., 2020), and increased likelihood of surgical site infections previously (Ahern et al., 2010). Surgery duration is affected by multiple factors including but not limited to surgeon experience, the surgical team and operating facility, and the severity of injury and full exploration of this is beyond the scope of this thesis. However, a practical recommendation for clinicians is to take steps to reduce surgery duration where possible. A recent systematic review identifies numerous strategies to reduce surgery duration in human oncology operations including fully preparing the patient, preparing the equipment and surgical instruments and using a surgical checklist to outline the plan and improve efficiency prior to the induction of the patient (Hoefsmit et al., 2021). These principles

are relevant across multiple species and hospitals are encouraged to audit and improve these processes to reduce their surgery durations.

As outlined in Chapter three, numerous factors that have been identified to be associated with poor outcomes previously were not found to be significant within the survival analysis. These included duration between injury and admission, performing surgery out of hours, bone or tendon involvement, and increasing number of surgical procedures. The relatively small numbers of cases contributing to these variables may mean a significant association was not identified with long term survival in this study. In addition, analysis of the return to athletic performance is warranted to assess whether these variables affect return to soundness rather than long-term survival. Furthermore, for true clarity to be gained on these factors, meta-analysis between multiple appropriately designed studies would allow the collation of cases to assess any true associations with outcome.

Features of study design

The features of research conduct identified in the scoping review were considered when designing the study investigating survival presented in Chapter three. Broad and transparent case inclusion criteria were used with descriptions of the number of parameters, the synovial fluid values chosen and descriptions for the cases included. A multi-centre prospective study design was used involving ten hospitals in the UK to generate representative results and maximise case numbers (Youssef et al., 2008). Prospective studies offer the advantage that tailored data collection forms can be made to investigate specific variables compared to retrospective studies that use hospital records to gather data (Song and Chung, 2010). Data capture forms were created based on important features of case presentation and treatment and these forms were piloted at one hospital prior to the start of recruitment. The outcome measured was chosen from previous criteria for reporting time frame to improve transparency and repeatability (Cook et al., 2010). A further area of analysis that would add significantly to the factors identified in this thesis, is the analysis of horses return to athletic function. This should be interpreted alongside survival data as even if a horse is alive, chronic lameness or loss of function would be considered a failure of treatment for most athletic animals (Cook et

al., 2010). This could provide vital information for clinicians and owners and further identify risk factors associated with poor outcomes.

Limitations

The results of this observational study, as with other veterinary epidemiological studies, are subject to selection bias (Dohoo, 2014, Hosgood and Scholl, 2001). Horses that were subject to euthanasia prior to or during the first treatment were excluded from analysis and omission of these cases may influence the true survival rate. In addition, only horses that were presented for treatment at hospitals were included. This could have influenced the survival rate and the risk factors identified. If horses that were too lame to travel to the hospital, or that had such severe injuries were euthanized on the surgical table, this could have altered the result leading to attrition bias (O'Connor et al., 2016). However, as the reasons for euthanasia are multifactorial involving owner, clinician and horse factors, it was chosen to investigate horses that were allowed an opportunity of treatment in this study.

The majority of this research has been conducted during the COVID – 19 pandemic. Case recruitment, case presentation and owner and clinician decision making could have been influenced by this and this effect is unknown. Further sources of selection bias were the loss of some cases to follow up. It was attempted to minimise follow up, and cases were contacted three times, and if non-response were categorised as lost to follow up. This resulted in 14% of cases being non-responders, which is considered acceptable for most response studies (Dettori, 2011).

Advanced survival analysis methods using multivariable Cox proportional hazards models were used in this study. This method was chosen to allow horses lost to follow up to contribute to the model during their known days of survival (Dohoo et al., 2009). Using other multivariable statistical techniques such as logistic regression, would result in censored horses being removed from analysis, whereas in survival analysis, every day a horses status is known as alive they can contribute to the analysis increasing the power of the results (Dohoo et al., 2009). This is especially important for studies with only a small number of

events or deaths, as in this study, with a 10.6% death rate. Other statistical methods that could have been utilised to further analyse this data include the use of frailty models. Frailty models can help describe the influence of unobserved covariates in a proportional hazards model and explain heterogeneity in variables (Dohoo et al., 2009) and could be used to analyse the models presented in Chapter three. This was beyond the remit of this thesis but could be considered for further work.

Summary of recommendations for future research

This thesis has identified several recommendations for further research and they are summarised below:

- Further studies investigating synovial sepsis using appropriate study designs, statistical methods and standardised reporting to increase the strength of the current body of evidence.
- Further validation of rapid diagnostic tests to improve patient side diagnosis of synovial sepsis.
- A consensus on a definition and criteria for cases of synovial sepsis to allow comparisons to be made between research groups so that systematic reviews and meta-analysis can be performed and guidelines for treatment be given in the future.
- Investigation of duration of antimicrobial therapy using randomised controlled clinical trials
- Investigation and clinical audit of factors affecting surgery duration in equine hospitals
- Analysis of return to athletic function after synovial sepsis treatment.

The results from this thesis have identified several risk factors associated with death after treatment with synovial sepsis to aid clinicians and owners in decision making and help improve welfare in regards to the treatment of synovial sepsis.

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GENERAL APPENDIX

University of Nottingham
UK | CHINA | MALAYSIA

Participant consent form

Investigating peri-operative factors associated with survival and return to athletic function of horses treated for synovial sepsis

Please read the accompanying client information sheet describing the study. By agreeing to participate, you approve and are consenting to the following:

	TICK BOX
I am over the age of 18 years' old	
I have read, or had read to me, the client information sheet and understand how this study works and have been able to ask any questions about my involvement	
I give consent for researchers to contact me for follow up information 1 year post-operatively which is essential for this study	
I understand and consent for my contact details (name and telephone number) to be collected by the primary researcher, safely stored on a password protected database and stored until follow up information is gathered, at which point it will be destroyed	
I give consent for the researchers to access and collect data about my horse's treatment of synovial sepsis	
I understand and consent for information collected about my horse to be kept strictly confidential, stored safely on a password protected database, and anonymised as soon as follow up information is gathered	
I understand that the anonymised data collected from this study will be used as part of a Masters of Veterinary Surgery qualification, published in scientific publications and used for further educational development	

FULL NAME	
HOME TELEPHONE NUMBER	
MOBILE NUMBER	
HORSE NAME	

SIGNATURE: _____ **DATE:** _____

University of Nottingham
UK | CHINA | MALAYSIA

Please fill in the below questionnaire. We would be grateful for any information you can provide us, but if you prefer to leave some answers blank then you can

CURRENT MAIN USE OF YOUR HORSE (please tick ONE main use)	☐ RETIRED or COMPANION ☐ HACKING & GENERAL USE ☐ SHOW JUMPING ☐ DRESSAGE ☐ EVENTING ☐ RACING	☐ HUNTING ☐ ENDURANCE **OTHER:**	
Description of current competition level: (e.g. BE100)			
IN YOUR OPINION, PRIOR TO THE SYNOVIAL SEPSIS INCIDENT: **1) IS YOUR HORSE CURRENTLY BEING USED FOR IT'S INTENDED PURPOSE?**			
☐ YES ☐ NO ☐ UNKNOWN	IF NOT, DETAILS		
2) HAS YOUR HORSE HAD ANY POOR PERFOMANCE ISSUES WITHIN LAST 6 MONTHS?			
☐ YES ☐ NO ☐ UNKNOWN	IF YES, PLEASE SPECIFY (e.g. EGUS, lameness issue)		
IS YOUR HORSE INSURED?	☐ YES ☐ NO ☐ UNKNOWN	**IF YES, COVERED FOR TREATMENT OF SYNOVIAL SEPSIS?**	☐ YES ☐ NO ☐ UNKNOWN
HOW MUCH IS YOUR HORSE INSURED FOR?		**WHAT DOES YOUR INSURANCE POLICY COVER?**	☐ MORTALITY ☐ VETS FEES ☐ BOTH ☐ NOT SURE

The completed form should be either:

- **Scanned and emailed to therese.desouza@bwequinevets.co.uk**
- **Posted to Therese de Souza, B&W Equine Vets, Breadstone, Berkeley, Gloucestershire, GL13 9HG**

An online version of this form can be found at www.ess.vet as well as further information on the study

Appendix 1: *Client consent form*

Appendix 2: *Data collection form*

SYNOVIAL SEPSIS DATA COLLECTION FORM

SECTION 1: HORSE AND OWNER DETAILS

OWNER FULL NAME			**HOSPITAL & INITIALS OF PERSON FILLING FORM OUT**		
HORSE NAME			**DATE OF ADMISSION**		**TIME OF ADMISSION (24hr)**
BREED		**AGE (years)**	**SEX**	☐ Gelding ☐ Mare ☐ Stallion	
WEIGHT Kgs (approx.)					

CURRENT MAIN USE OF THE HORSE (please tick ONE main use)	☐ RETIRED or COMPANION ☐ HACKING & GENERAL USE ☐ SHOW JUMPING ☐ DRESSAGE	☐ EVENTING ☐ RACING ☐ HUNTING ☐ ENDURANCE	**OTHER:**
Description of current competition level: (e.g. BE100)			

IN THE OWNER'S OPINION, PRIOR TO THE SYNOVIAL SEPSIS INCIDENT:

1) IS THE HORSE CURRENTLY BEING USED FOR IT'S INTENDED PURPOSE?

☐ YES ☐ NO ☐ UNKNOWN	**IF NOT, DETAILS**

2) HAS THE HORSE HAD ANY POOR PERFOMANCE ISSUES WITHIN THE LAST 6 MONTHS?

☐ YES ☐ NO ☐ UNKNOWN	**IF YES, PLEASE SPECIFY (e.g. EGUS, lameness issue)**

IS THE HORSE INSURED?	☐ YES ☐ UNKNOWN ☐ NO	**IF YES, COVERED FOR TREATMENT OF SYNOVIAL SEPSIS?**	☐ YES ☐ UNKNOWN ☐ NO
HOW MUCH IS THE HORSE INSURED FOR?		**WHAT DOES THE INSURANCE POLICY COVER?**	☐ MORTALITY ☐ BOTH ☐ VETS FEES ☐ NOT SURE

SECTION 2: CLINICAL DETAILS AT PRESENTATION

WHEN DID INJURY OCCUR PRIOR TO REFERRAL? (in hours)		**OR IF UNKNOWN, WHEN WAS HORSE LAST SEEN NORMAL? (DATE)**	
DEGREE OF LAMENESS (AAEP 0-5)		**PRIMARY LIMB AFFECTED:**	☐ LF ☐ RF ☐ LH ☐ RH
PRIMARY SYNOVIAL STRUCTURE AFFECTED:		**OTHER SYNOVIAL STRUCTURE(S) AFFECTED ON PRIMARY LIMB:**	☐ YES **DETAILS:** ☐ NO
SECONDARY LIMB AFFECTED?	☐ LF ☐ RF ☐ LH ☐ RH ☐ N/A	**SYNOVIAL STRUCTURE(S) AFFECTED ON SECONDARY LIMB:**	
CAUSE OF INJURY FOR PRIMARY SYNOVIAL STRUCTURE (please tick as many as appropriate)	☐ KICK ☐ WIRE ☐ COLLISION/TRAUMA ☐ LOCAL SPREAD (e.g. cellulitis)	PUNCTURE INJURY: ☐ THORN ☐ FOREIGN BODY ☐ OTHER: ☐ HAEMATOGENOUS	☐ UNKNOWN ☐ IATROGENIC **OTHER:**

IF WOUND PRESENT, DESCRIPTION:

SIZE (mm)	**DEPTH**	**DEGREE OF CONTAMINATION:**	**HAEMORRHAGE:**	**EPITHELIASIATION:**
	☐ Superficial ☐ Partial skin thickness ☐ Full skin thickness ☐ Obvious visualisation of deeper tissues	☐ MILD ☐ MODERATE ☐ SEVERE ☐ NONE ☐ UNKNOWN	☐ MILD ☐ MODERATE ☐ SEVERE ☐ NONE ☐ UNKNOWN	☐ NONE PRESENT NEW EPITHELIUM COVERING WOUND: ☐ 0-25% ☐ 25-50% ☐ 50-75% ☐ 75-100%

DISCHARGE DESCRIPTION:	**AMOUNT OF DISCHARGE:**	**PERIPHERAL SKIN EDEMA:**	**OTHER DETAILS:**
☐ NONE ☐ HAEMORRHAGIC ☐ SUSPECTED SYNOVIAL FLUID ☐ SEROSANGUINOUS ☐ PURULENT	☐ NONE ☐ SCANT ☐ SMALL ☐ MODERATE ☐ LARGE	☐ NONE ☐ MILD ☐ MODERATE ☐ SEVERE	

SYNOVICENTESIS DETAILS:

WHERE WAS THE SAMPLE TAKEN?	**WCC :** x10^9 cells/L	**TP:** g/dl	**WAS A CULTURE & SENSITIVITY TAKEN?**	☐ YES ☐ NO ☐ UNKNOWN
☐ HOSPITAL ☐ RVS ☐ NOT TAKEN	PMN %:	VOLUME: mls		

WERE ANY OTHER DIAGNOSTICS PERFORMED? (e.g. pressure distension test, probe)	**ANY OTHER DETAILS:**

i) PRIOR TO REFERRAL, DID THE HORSE RECEIVE:

ANALGESIA?	☐ YES ☐ UNKNOWN ☐ NO	DETAILS OF DRUG(S), ROUTE, DOSAGE:		
SYSTEMIC ANTIMICROBIALS?	☐ YES ☐ UNKNOWN ☐ NO	DETAILS OF DRUG(S), ROUTE, DOSAGE:		
REGIONAL ANTIMICROBIALS?	☐ YES ☐ UNKNOWN ☐ NO	METHOD: ☐ IVRP (intra-venous) ☐ IOP (intra-osseous) ☐ INTRASYNOVIAL OTHER:	**DRUG:** **SITE:**	**DOSE:** **VOLUME:**

ii) AFTER ADMISSION AND PRIOR TO SURGICAL TREATMENT, DID THE HORSE RECEIVE:

ANALGESIA?	☐ YES ☐ UNKNOWN ☐ NO	DETAILS OF DRUG(S), ROUTE, DOSAGE:		
SYSTEMIC ANTIMICROBIALS?	☐ YES ☐ UNKNOWN ☐ NO	DETAILS OF DRUG(S), ROUTE, DOSAGE:		
REGIONAL ANTIMICROBIALS?	☐ YES ☐ UNKNOWN ☐ NO	METHOD: ☐ IVRP (intra-venous) ☐ IOP (intra-osseous) ☐ INTRASYNOVIAL OTHER:	**DRUG:** **SITE:**	**DOSE:** **VOLUME:**

iii) IMAGING FINDINGS:

WHAT DIAGNOSTIC IMAGING WAS PERFORMED? (tick those performed)			
☐ RADIOGRAPHY ☐ ULTRASOUND ☐ MRI	☐ CT ☐ SCINTIGRAPHY	☐ NONE OTHER:	
FROM RADIOGRAPHIC EXAM, WHICH OF THE FOLLOWING WERE DIAGNOSED? (TICK AS MANY AS APPORPIATE)	☐ NO ABNORMALITIES ☐ FOREIGN BODY ☐ GAS TRACKING ☐ SOFT TISSUE SWELLING ☐ SYNOVIAL EFFUSION ☐ WOUND	REACTIVE PERIARTICULAR ACTIVITY ☐ OSTEOPHYTE ☐ ENTHESIOPHYTE ☐ PERIOSTEAL PROLIFERATION	☐ OSSEOUS DEFECTS: ☐ FRACTURE ☐ FRAGMENTATION ☐ OSTEITIS ☐ OSTEOMYELITIS ☐ SEQUESTRUM
FROM THE ULTRASONOGRAPHIC EXAM, WHICH OF THE FOLLOWING WERE DIAGNOSED? (TICK AS MANY AS APPORPIATE)	☐ NO ABNORMALITIES ☐ EFFUSION OF SYNOVIAL STRUCTURE ☐ SYNOVIAL THICKENING ☐ FOREIGN BODY/MATERIAL ☐ FIBRINOUS LOCULATIONS ☐ DEFECT IN BONE SURFACE ☐ DEFECT IN ARTICULAR CARTILAGE	PARTIAL LACERATION: ☐ SDFT ☐ DDFT ☐ SUSPENSORY LIGAMENT COMPLETE LACERATION: ☐ SDFT ☐ DDFT ☐ SUSPENSORY LIGAMENT	
OTHER DETAILS RELEVANT FROM IMAGING:			

SECTION 3: INTRA-OPERATIVE INFORMATION

DATE OF SURGERY and INTIALS OF SURGEON	**TIME OF SURGERY:**	**ANAESTHESIA:**
	☐ WORKING HOURS (8am-6pm) ☐ OOH **SPECIFY (24hr):**	☐ GENERAL ANAESTHESIA ☐ STANDING SEDATION

PRIMARY SURGERY- IN EACH CATEGORY PLEASE TICK ONE AND ADD DETAILS AS NECESSARY:

LAVAGE TECHNIQUE:	**DRAINAGE:**	**INDWELLING ANTIMICROBIALS IMPLANTS LEFT INSITU:**
☐ THROUGH AND THROUGH NEEDLE LAVAGE ☐ ENDOSCOPIC LAVAGE ☐ OPEN APPROACH (E.G. ARTHROTOMY) **DETAILS:**	☐ NO DRAINAGE PASSIVE: ☐ WOUND LEFT OPEN ☐ INTRASYNOVIAL CATHETER ☐ OTHER DRAIN TYPE (E.G. PENROSE) ACTIVE ☐ CLOSED SUCTION (E.G. JACKSON PRATT)	☐ NONE ☐ PMMA BEADS ☐ ANTIMICROBIAL IMPREGNANTED COLLAGEN SPONGES **OTHER:**

IF LAVAGE PERFORMED WHAT TYPE OF FLUID WAS USED? Any additives?		**APPROX. VOLUME OF FLUID USED (litres)**	
HOW MANY PORTALS INTO THE SYNOVIAL STRUCTURE WERE MADE?	☐ 1 ☐ 3 ☐ 2 ☐ 4 OTHER:	**PORTAL CLOSURE SUTURE MATERIAL TYPE AND SIZE:**	**PORTAL CLOSURE SUTURE PATTERN:**

FINDINGS AT SURGERY: (please describe detail as you would for a surgical report)	TENDON, LIGAMENT OR OTHER SOFT TISSUE PATHOLOGY:	SYNOVIAL CHANGES: ☐ PROLIFERATION ☐ HYPERAEMIA ☐ PETECHIATION ☐ STUNTED VILLI Evidence of pannus? ☐ MILD ☐ MODERATE ☐ MARKED	BONE AND CARTILAGE PATHOLOGY: CARTILAGE EROSIONS ☐ PARTIAL THICKNESS ☐ FULL THICKNESS ☐ FOCAL ☐ EXTENSIVE BONE ☐ OSTEOCHONDRAL FRAGMENTS ☐ OSTEITIS/OSTEOMYELITIS ☐ SUBCHONDRAL BONE DEFECTS ☐ OSSEOUS DAMAGE (w/o fragmentation)	☐ Foreign material DETAILS:

WERE ANTIMICROBIALS GIVEN INTRA-OPERATIVELY?			
☐ SYSTEMIC ☐ NO ☐ REGIONAL ☐ UNKNOWN ☐ BOTH	SYSTEMIC DETAILS:	Drugs(s) route and dosage:	
	REGIONAL DETAILS:	☐ IVRP (intra-venous) ☐ INTRASYNOVIAL ☐ IOP (intra-osseous) OTHER:	

IF A WOUND WAS PRESENT, WAS THIS RESECTED?	☐ YES ☐ NO	IF A WOUND WAS PRESENT, WAS IT CLOSED?	☐ SUTURES ☐ LEFT OPEN ☐ STAPLES DETAILS:

HOW WAS THE WOUND DEBRIDED/RESECTED?	☐ SURGICAL/SHARP ☐ MECHANICAL (wet to dry or pressured lavage) ☐ HYDROSURGERY (e.g. Versajet system) ☐ ENZYMATIC or CHEMICAL ☐ OTHER:	ANY OTHER SURGICAL DETAILS?	

SECTION 4: POST OPERATIVE INFORMATION

WAS THE HORSE MAINTAINED ON ANTIMICROBIALS POST OPERATIVELY?					
SYSTEMIC? ☐ UNKNOWN ☐ YES ☐ SAME AS PRE-OP ☐ NO	Drug(s), route, dose:		DURATION OF TREATMENT (NO. DAYS POST SURGERY):		
REGIONAL? ☐ NO ☐ YES ☐ UNKNOWN	NUMBER OF TREATMENTS:	☐ IVRP (intra-venous) ☐ IOP (intra-osseous) ☐ INTRASYNOVIAL OTHER:	DRUG:	DOSE:	
			SITE:	VOLUME	

WAS THE HORSE MAINTAINED ON ANALGESIA POST OPERATIVELY?	
☐ YES ☐ NO ☐ UNKNOWN	Drug (s), route, dose, volume: Which day(s) post sx.?

BACTIERAL CULTURE RESULTS:					
POSITIVE CULTURE? ☐ NO ☐ UNKNOWN ☐ YES	SPECIES IDENTIFIED:		WAS ANTIMICROBIAL RESISTANCE SHOWN? ☐ NO ☐ DETAILS: ☐ YES		
WAS ANTIMICROBIAL THERAPY CHANGED CONSIDERING C+S RESULTS?					
☐ YES ☐ UNKNOWN ☐ NO	DETAILS OF CHANGE:				

IF REPEAT SYNOVIOCENTESIS AND LAMENESS GRADING WAS PERFORMED, PLEASE FILL IN TABLE BELOW:					
	NUMBER OF DAYS POST SURGERY				
WCC (x10³ cells/L)					
TP (g/dL)					
LAMENESS (0-5 AAEP)					

SECTION 5: DISCHARGE AND SURVIVAL

WERE MULTIPLE SURGERIES REQUIRED?			
☐ YES ☐ UNKNOWN ☐ NO	IF YES, NUMBER AND TYPE OF EXTRA SURGERIES PERFORMED:		

DID THE HORSE SURVIVE GA?	☐ YES ☐ UNKNOWN ☐ NO	IF EUTHANASED, WHY?	
DID THE HORSE SURVIVE TILL DISCHARGE?	☐ YES ☐ UNKNOWN ☐ NO	NO. DAYS OF HOSPITALISATION:	
WAS THE HORSE DISCHARGED ON ANY MEDICATION?	☐ YES ☐ UNKNOWN ☐ NO	DETAILS: DRUG(S) AND DOSE, DURATION, WHY?	

Important information:

- Only authorised researchers working at the University of Nottingham's School of Veterinary Medicine and Science will have access to information collected during the analysis stage.
- Anonymised results of this study will form part of the principal researcher's Masters of Veterinary Surgery qualification and will be published in relevant scientific publications, presented at research conferences or shared with select veterinary practices.
- **Your participation is completely voluntary**, and if at any point you wish to withdraw from the study with no explanation you can.

If you have any questions about the project or would like further information, please contact:

Therese de Souza MA VetMB MRCVS

Telephone: 07870408799
Email:equinesynovialsepsis@gmail.com
Website: www.ess.vet

University of Nottingham
UK | CHINA | MALAYSIA

SYNOVIAL SEPSIS STUDY

An investigation into risk factors associated with horses being treated for synovial sepsis

Study based at the University of Nottingham

This research study has been approved by the School of Veterinary Medicine and Science's ethics committee.

What is synovial sepsis and how does it occur?

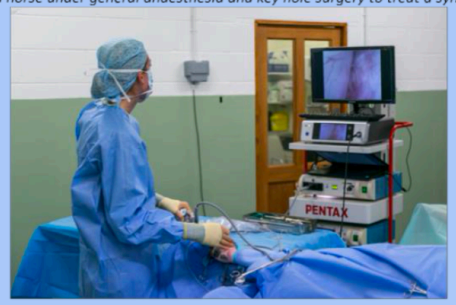
Synovial sepsis describes when infection enters a structure containing synovial fluid. These synovial structures can include either joints, tendon sheaths (sleeves of tissue in which tendons run) or bursas (bags of fluid in which tendons run over bone). Infection can enter in several different ways including:

- a wound overlying one of these structures,
- a puncture injury where no obvious wound is present
- local spread from neighbouring infected tissue
- from the blood stream *(seen more in foals than adult horses)*

What are the clinical signs?

When infection takes hold it causes dramatic inflammation within the synovial structure, changing the consistency and amount of synovial fluid. This can cause distension of the synovial structure, extreme pain and severe lameness. In the long term this can cause chronic changes to the synovial structure leading to loss of function and long term lameness.

Image below shows a horse under general anaesthesia and key hole surgery to treat a synovial infection



How is synovial sepsis treated?

There are several different techniques to treat synovial infections however the basic principles include:

- lavage of the synovial structure
- antimicrobial treatment
- anti-inflammatory treatment
- box rest and rehabilitation

Outcome after synovial sepsis

Synovial sepsis is a serious condition. If the infection is eliminated and there is no significant injury to any important tissues (e.g. bone, joint surface or tendon) then the horse should make a full recovery. If there is injury to underlying structures this can impact on the outcome and increase the rehabilitation period. If the infection is not controlled, then a repeat surgery or euthanasia will need to be among the considerations.

What are we investigating?

We aim to investigate factors affecting survival to discharge from the hospital and return to athletic function after synovial sepsis. Identification of risk-factors for poor prognosis will benefit owners and vets and improve outcomes for horses in the future.

Study outline:

- All owners with horses undergoing synovial sepsis treatment are invited to participate
- **You will need to sign our consent form either on paper or online and provide your contact details (name and telephone number)** for us to contact you for follow-up information. This is very important.
- Your vet will fill out a short form describing clinical information about your horse and their treatment

Information about your contact details:

- Any information about you and your horse will be handled in the strictest confidence
- We require your contact details which will be collected at the start of the study, safely stored in a secure office on a password protected database by the primary researcher, and destroyed once the follow up information has been gathered.
- We also will be collecting clinical information about your horse which will be stored on a password protected database and anonymised as soon as the follow up information is gathered.

Appendix 4: *Telephone questionnaire*

Telephone questionnaire

Hello (**CLIENT NAME**) my name is (**YOUR NAME**) from (**HOSPITAL NAME**). I am contacting you to ask some questions regarding your horse (**HORSE'S NAME**) that was treated for an infected joint/tendon sheath. Is it a good time to speak? We are doing a follow up questionnaire after synovial sepsis treatment that will take approximately 5 minutes of your time.

This information will be used to help evaluate and improve treatment and outcomes after synovial sepsis. Information collected will be anonymised. At any time during the survey period (February 2021-February 2022) if you would like to amend your responses, or withdraw from participation in the project, please do not hesitate to contact me, using the contact details provided on the information letter.

SECTION 1: HORSE AND OWNER DETAILS

Owner full name		**Hospital involved**			
Horse name		**Date of interview**		**Time of interview**	
Person filling out form		**Details of contact attempts**			
Are any details needed from recruitment stage? (e.g. signalment of horse, cause of injury, etc.)					

SECTION 2: SURVIVAL AND OWNERSHIP

Do you still own your horse?		
☐ YES ☐ NO ☐ UNKNOWN	**DETAILS**	
Is the horse alive?		
☐ YES ☐ NO ☐ UNKNOWN	**DATE OF DEATH:**	**DETAILS:**
If the horse has died - Was this related to the synovial sepsis injury?		
☐ YES ☐ NO ☐ UNKNOWN	**CAUSE OF DEATH:**	**DETAILS:**

SECTION 3: LEVEL OF WORK PRIOR TO INJURY (*if not previously answered on consent forms)*

What did you use (X) for prior to the synovial sepsis injury?	☐ RETIRED or COMPANION ☐ HACKING & GENERAL USE ☐ SHOW JUMPING ☐ DRESSAGE	☐ EVENTING ☐ RACING ☐ HUNTING ☐ ENDURANCE	**OTHER:**
Description of competition level prior to injury: (e.g. BE100)			
In your opinion, prior to the synovial sepsis incident: **1) Was (X) being used for (his/her) intended purpose?**			
☐ YES ☐ NO ☐ UNKNOWN	**IF NOT, DETAILS**		
2) Did (X) have any poor performance issues within the last 6 months prior to surgery?			
☐ YES ☐ NO ☐ UNKNOWN	**IF YES, PLEASE SPECIFY (e.g. EGUS, lameness issue)**		

SECTION 4: LEVEL OF WORK >1 YEAR AFTER INJURY

What is the current main use of (X)?	☐ RETIRED or COMPANION ☐ HACKING & GENERAL USE ☐ SHOW JUMPING ☐ DRESSAGE	☐ EVENTING ☐ RACING ☐ HUNTING ☐ ENDURANCE	**OTHER:**
Description of current competition level: (e.g. BE 100)			
In the owner's opinion, after the synovial sepsis incident: **Is (X) currently being used for its intended purpose?**			
☐ YES ☐ NO ☐ UNKNOWN	**IF NOT, DETAILS**		
Has (X) returned to a lower, equal or greater level of performance after the synovial sepsis injury?			
☐ LOWER ☐ EQUAL ☐ GREATER ☐ UNKNOWN	**DETAILS**		
Do you feel that the synovial sepsis injury prevented or limited your horse's performance?			
☐ YES ☐ NO ☐ UNKNOWN	**IF NOT, DETAILS**		
Has (X) had any other poor performance issues since the synovial sepsis incident?			
☐ YES ☐ NO ☐ UNKNOWN	**IF YES, PLEASE SPECIFY (e.g. EGUS, lameness issue)**		

SECTION 5: REHABILITATION

How long was (X) out of work for after the synovial sepsis injury? (Weeks or Months)			
In your opinion, was the period of time the horse was out of work after synovial sepsis injury shorter, longer or as expected?			
☐ SHORTER ☐ LONGER ☐ AS EXPECTED ☐ UNKNOWN	**Details:**		
Did you do any specific rehabilitation after the injury? (tick those applicable)	☐ BOX REST ☐ WALKING EXERCISE ☐ RE-EXAMINATIONS DETAILS:	☐ PHYSIOTHERAPY EXERCISES (e.g. stretches/manipulations) ☐ MASSAGE ☐ ACUPUNCTURE	☐ SUPPLEMENTS ☐ UNKNOWN OTHER:
Is (X) currently receiving any on-going medications after the infection?			
☐ YES ☐ NO ☐ UNKNOWN	**DETAILS**		

Thank you for your time and for participating in this study.

Appendix 5: *Material published during the writing of this thesis*

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EVIDENCE REVIEW

Equine Veterinary Journal WILEY

A scoping review of the current evidence on treatment and outcomes following synovial sepsis

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School of Veterinary Medicine and Science, University of Nottingham.

Summary

Background: Synovial sepsis is a frequent cause of morbidity and mortality in horses. Despite advances in diagnostics and treatments, persistent infection or chronic lameness can occur.

Objectives: To perform a scoping review to identify and evaluate the current evidence on the factors implicated in the success of treatment for synovial sepsis.

Study design: Joanna Briggs Institute scoping review.

Methods: A protocol was registered, and a systematic literature search was performed on CAB abstracts, Medline, Scopus and Embase. Inclusion and exclusion criteria were developed and studies systematically reviewed against this. Studies relating to factors affecting treatment success following synovial sepsis were retained and data was extracted on study method, population characteristics and factors significantly associated with treatment outcome.

Results: In total, 2338 studies were identified, and 61 were included to full paper analysis. Eight papers reported significant factors, identifying 15 risk factors associated with two measurements of outcome, either survival and/or return to athletic function. The 15 factors were identified and categorised into pre-, intra- and post-operative factors. Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology, and the use of systemic antimicrobials. There were many discrepancies in inclusion criteria of cases of synovial sepsis as well as measurement and description of outcome variables.

Main limitations: Non–English language studies or conference proceedings were not included. Only small numbers of papers had similar findings.

Conclusions: Standardisation of inclusion criteria is essential to enable comparisons and analysis between studies on synovial sepsis. Future studies should use methodologies to reduce bias including multicentre and multinational studies, prospective study design and robust statistical modelling.

KEYWORDS

horse, outcome, prognosis, return to athletic function, scoping review, survival, synovial sepsis

The abstract is available in Portuguese in the Supporting Information section of the online version of this article.

1 | INTRODUCTION

Synovial sepsis is an important condition affecting the welfare of horses and can result in mortality or loss of athletic performance. In a clinical setting, gold standard treatment aims for the rapid elimination of infection within the synovial structure by early identification, large volume lavage, debridement and systemic and regional antimicrobial use. Previously, studies investigating survival to discharge after synovial sepsis have reported wide ranges of outcomes (56%-100%).[1-11] There is similar variation for reported rates of horses returning to athletic function (36%-94%).[1,4,7,9-13] These findings highlight that horses can have a successful outcome, but despite gold standard treatment, there are cases where synovial sepsis leads to death or ongoing lameness, and significant financial implications for owners.

Anecdotally, there appears to be a lack of consensus on how different aspects of synovial sepsis treatment affect outcome. For example, some studies have reported that the duration of clinical signs, prior to referral, significantly affected outcome[1,3,6] where others found no significant association.[2,4,7,10,13,14] Similarly, the findings regarding the use of regional antimicrobials are inconclusive with a positive association between use of regional limb perfusion and survival reported in some studies[14] and a negative association reported elsewhere.[10] In addition, different inclusion criteria for synovial sepsis cases and for measurements of treatment outcome are used between research groups.[1,2,9-11,15] Variation in inclusion criteria results in different subsets of horses being given a diagnosis of synovial sepsis and being subsequently investigated making comparisons between study results challenging. This perceived lack of clarity over key definitions and outcome variables, as well as the broad distribution of publications lends this body of literature to a scoping review.

There are many different types of evidence synthesis reviews that can be used to search, appraise and present the literature including but not limited to systematic reviews, meta-analysis, rapid reviews and scoping reviews.[16] There are currently no structured peer-reviewed articles, which describe a systematic search and collation of current evidence investigating synovial sepsis, with only traditional subjective narrative reviews within the literature.[17-19] Systematic reviews are the most commonly used evidence synthesis technique and are widely used within a human healthcare setting.[20] Through structured and transparent searching and analysis of the literature they minimise bias and can provide conclusions, which can influence practice and policy[20,21]; however, systematic reviews are targeted towards answering a specific question. Where discrepancies in studied populations exist within the literature, or when the number and type of relevant studies is unknown, the usefulness of this evidence synthesis technique is reduced.

A scoping review provides an alternative but similarly objective methodology as well as a broad overview of a specific topic.[22] Scoping reviews do not perform any critical analysis of the studies identified, instead through methodological and rigorous peer-reviewed database searching they produce a map of the literature and can identify and clarify key concepts and definitions through extensive charting. In addition, they can investigate research conduct and can recognise knowledge gaps in a body of literature.[21,22] A scoping review can be performed to assess feasibility and, if then appropriate, to identify specific questions prior to performing a detailed systematic review.[23-25] For these reasons, scoping reviews are gaining popularity as an evidence synthesis tool within equine veterinary research.[25-27]

This scoping review aimed to identify and evaluate the current literature available on treatment for synovial sepsis in the horse, including outcomes following different treatment options, and factors associated with the success and failure to respond to treatment. In addition, this scoping review aimed to identify the feasibility and areas appropriate for a future systematic review.

The objectives of this scoping review were as follows:

- To identify the published peer-reviewed literature on the treatment for synovial sepsis in the horse through a systematic search of the databases.
- To extract and chart key data on study characteristics and results for outcome of synovial sepsis in the horse, including survival and return to work.
- To identify any gaps in knowledge in relation to the treatment and outcomes of synovial sepsis.
- To categorise and summarise factors that affect the treatment success in terms of survival and return to work.

2 | MATERIALS AND METHODS

The Preferred Reporting Items for systemic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) framework was used for this scoping review.[28] This review was registered to an existing protocol (https://osf.io/5sbfk/?view_only=586e7b672deb4342b48da842c9dcb721). All authors and a university librarian provided input and review of the database search strategy. The review was conducted in duplicate by two researchers, one of whom has completed the Joanna Briggs Institute accredited training programme. Any disagreements between the two researchers were decided by a third independent reviewer.

2.1 | Eligibility criteria

Inclusion and exclusion criteria were created to facilitate assessment and appraisal of the titles, abstracts and studies identified and are described in Table 1. Broad inclusion criteria to capture appropriate literature were used. Horses were included if they were greater than 6 months old.

2.2 | Information sources and search strategy

The initial search strategy was performed on 19 May 2020 and updated on 22 September 2020 using Medline In-Process & Non-Indexed

TABLE 1 Inclusion and exclusion criteria for a scoping review of the literature on synovial sepsis in the horse

Criteria	Inclusion	Exclusion
Case	Domesticated adult equids (Horses and ponies)	Donkeys and zebra Foals <6 months and neonates
Exposures	Synovial sepsis of a bursa, tendon sheath or joint	
Intervention	Either medical or surgical treatment[a] for synovial sepsis including lavage, systemic or regional antimicrobials, drainage, use of an implant, specific surgical technique	Papers not relating to treatment
Outcome	Success of treatment – with a focus of either survival[b] and/or return to work[c]	
Language	English or papers with translation available	Translation not available
Study design	Case series, cohort, case control and cross-sectional studies	Narrative, text book chapters, individual case reports
Publication type	Peer reviewed journals Conference proceedings	Unable to obtain full study details Non-peer-reviewed journals Papers published before 1980

[a]Treatment definitions: Lavage – the washing out of a synovial structure with a fluid. Systemic antimicrobials – the administration of antimicrobials via intramuscular, intravenous, oral or subcutaneous routes. Regional antimicrobials – the administration of antimicrobials to a local regional or specific synovial cavity (eg intravenous limb perfusion, intrasynovial injection, intraosseous injection etc). Drainage – systematic withdrawal of fluids and discharges from a synovial cavity. Implant – a material surgically inserted into a tissue for a specific function. Specific surgical technique – details of a novel or specific treatment technique provided.

[b]Survival – included the horse survival to discharge and to other post-operative time points.

[c]Return to work was used as an umbrella term, as decided by the researchers, to include studies relating to any of the following subjective measurements of acceptable function: return to athletic function, return to previous athletic function, return to work.

Citations and Ovid MEDLINE (1946 – present), CAB Abstracts (1973 – present), Scopus Abstract and citation search (1966 – present) and Embase (1974 – present), which include those that are recommended for searching veterinary literature.[29] No date restriction was applied to the search. All references were downloaded and managed in Endnote reference manager (Endnote X9.3.2, Clarivate Analytics).

Search combinations were constructed from the following components using a PICO search strategy:

A exp horses/
B (horse* or pony or ponies or equine or equidae).mp.
C exp sepsis/
D (sepsis or septic).mp
E exp synovial sheaths/
F exp synovial fluid/
G exp tenosynovitis/
H exp tendon/
I exp infection/
J infection*.mp
K ("synovial sepsis" OR "synovial septic" OR "septic arthrit*" OR synovitis).mp
L ((infection* or sepsis or septic) adj3 (synovial or tenosynovitis or bursa* or bursitis or tendon* or joint* or synovium or arthritis)).mp

2.3 | Selection of sources of evidence

The studies were systematically appraised in several steps. Duplicate studies were removed by the primary researcher and titles were assessed by two researchers. Studies were retained if they contained terms relating to outcomes following synovial sepsis, and if this was ambiguous or unclear, the titles were retained to the next stage (abstract review). The abstracts were then independently appraised based on the inclusion and exclusion criteria outlined in Table 1 by two researchers; these were then discussed, with any ambiguous studies taken forward to full text assessment. The studies taken forward to full text assessment were appraised by one researcher based on the inclusion and exclusion criteria, and this was validated by a second researcher to result in a final list of full text studies.

2.4 | Data charting

The full text studies were analysed and relevant data extracted into charts by the primary researcher. Chart headings, publication categorisation and classification was decided and a consensus reached after discussion with all researchers. Study characteristic data were extracted under the following headings: author, year, geographical location, aims, sample size, treatment investigated, outcomes measured and significant outcomes. Treatment data were charted into categories if studies described techniques including: lavage, systemic antimicrobials, regional antimicrobials, drainage, use of an implant, specific surgical technique or treatment not specified. Outcomes measured were classified into either survival and/or return to work; if this was not clearly specified within the publication, then it was discussed between the researchers and a category assigned. Those studies with multivariable statistical analysis of outcome variables were grouped and categorised. Following study characteristic analysis, the studies were charted to include synovial

structure, inclusion criteria, variable investigated, author and measure of association. Inclusion criteria were charted to include the number of diagnostic criteria specified, synovial fluid parameters, direct communication with a synovial structure, subjective assessment of cases and any other details. Case series with no statistical analysis were also categorised dependent on synovial structure and charted to include synovial structure, author, aims and key findings. No additional methodological quality or risk of bias assessment was performed in line with scoping review protocol.[28]

3 | RESULTS

3.1 | Selection of sources

A total of 2338 studies were identified on the initial database searches. Figure 1 highlights the flow diagram of publication handling and assessment as outlined in the selection of sources of evidence. There were 111 studies, which met inclusion criteria for full text assessment; full text scripts were not available for 15 studies with 12 being abstracts from conference proceedings with no corresponding full text, and three were not available. After full text assessment of the remaining studies, nine experimental studies were identified,[30-38] which induced synovial sepsis and investigated specific treatment techniques or changes in diagnostic parameters over a short period (less than 21 days or not specified). These were excluded from further analysis. Other studies were excluded due to language (10), outcome (4), exposure (3) and intervention (2). There were 61 studies that met the final inclusion criteria and data are presented in Table S1 comparing study characteristics, population characteristics as well as significant risk factors identified.

3.2 | Characteristics of sources of evidence

From the 61 included studies, there were 23 studies based in the USA, 18 studies based in the UK, four studies based in Australia, three studies based in Belgium and Canada, and two studies based in Egypt. One study was conducted in each of the following countries: Austria, Germany, Israel, Netherlands, Spain, New Zealand and Ireland. Figure 2 demonstrates the case number of the studies, showing that 49/61 (80.3%) studies had between 1-60 subjects with 12/61 (19.7%) studies having more than 61 subjects. Most studies were based at one equine hospital (42/61, 68.9%), or two hospitals (9/61, 14.8%), and the remaining studies being based at more than two hospitals (7/61, 11.5%) or not specified (3/61, 4.9%).

The most frequent type of study designs were retrospective case series (26/61) and retrospective cross-sectional studies (26/61)

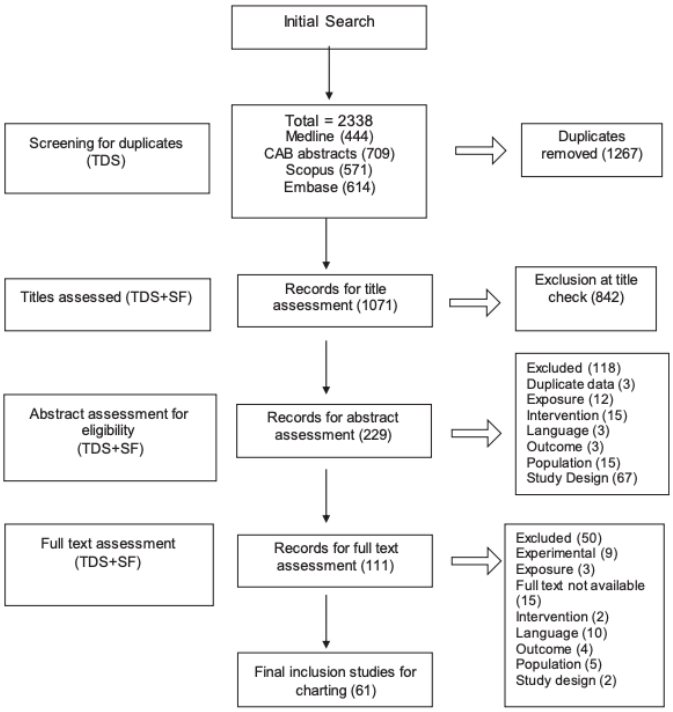

FIGURE 1 Flow diagram outlining the process used to identify studies on outcomes after synovial sepsis following systematic review of the available literature. Initials relate to authors: TDS, Therese de Souza; SF, Sarah Freeman

followed by retrospective cohort (4/61), prospective case series (3/61), prospective observational (1/61) and retrospective case-controlled studies (1/61). Figure 3 demonstrates the different study types plotted dependent on publication date in 5-year ranges.

Of the treatments techniques described within the studies, a combination of lavage, systemic and regional antimicrobials was described in 54/61 studies, and drainage was described in 20/54 of these studies. A specific surgical technique or surgical implant was described in 21/61 and 13/61 studies.

Within these 61 studies, eight investigated outcomes following synovial sepsis using multivariable analysis. The inclusion criteria of these eight studies and the reported results are presented in Table 2 and 3, respectively. Eighteen studies did not use a multivariable analytical approach but used different statistical analysis (15/18) to investigate outcome and the results are presented in Table S2. Three studies (3/18) found no statistically significant data on outcome and were not included.[7,39,40] Descriptive case series that reported outcomes on specific causes, treatment techniques or specific synovial structures are presented in Table S3.

Other small groups and themes of studies were identified. There were six studies that investigated the prevalence of synovial sepsis after iatrogenic intervention and reported the outcome of these horses.[41-46] All six studies had small numbers of horses (range 3-16), and no statistical analysis was performed on outcome for any of the studies. One study specifically described treatment for horses with blackthorn synovitis,[47] and one study identified outcomes in working equids.[48]

3.3 | Results of individual sources

Eight studies investigated outcome following synovial sepsis using multivariable analysis, and Table 2 presents the inclusion criteria specified within the eight studies. One study included descriptive details of the diagnosis of synovial sepsis.[10] Seven studies specified different values of synoviocentesis parameters for the diagnosis of cases of synovial sepsis including the white blood cell count (range 5-30 × 10^9 cells/L), with five of these studies further specifying a percentage of polymorphonuclear cells (80%-90%)[2,9,11,14,49] and six studies identified different total protein concentrations (range 20-40 g/L).[1,2,9,11,14,49] Five studies identified a positive bacterial culture, and[2,9,11,14,49] two identified cytological features of

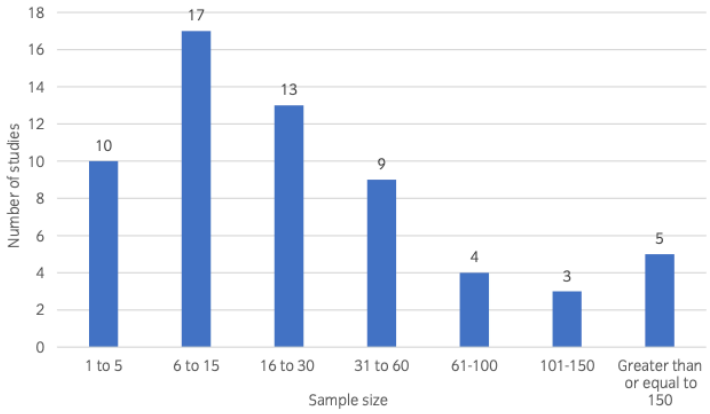

FIGURE 2 Chart to show the number of studies with different sample sizes identified for a scoping review of outcomes after synovial sepsis

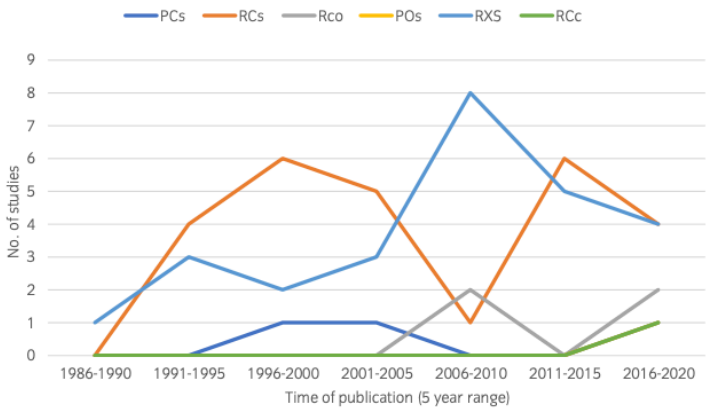

FIGURE 3 Chart to show the trend of different publication types of the studies identified from a scoping review of outcomes after synovial sepsis between the years 1986-2020. Abbreviations: PCs, prospective case series; POs, prospective observational study; RCc, retrospective case-controlled study; Rco, retrospective cohort study; RCs, retrospective case series; RXS, retrospective cross-sectional study

TABLE 2 Inclusion criteria specified by the studies, which reported risk factors affecting outcome after synovial sepsis in the horse

		Synovial fluid analysis								
Author	Number of criteria specified	Gross appearance of SF	Nucleated cell count	% of PMN	Total protein concentration	Positive bacterial culture	Cytological examination	Wound/direct communication	Subjective assessment	Other details
Crosby et al	X	X	≥30 x 10^9 cells/L	>80%	≥30 g/L	√	X	√	X	
Findley et al	X	X	>20 x 10^9 cells/L	X	>20 g/L	X	X	√	X	
Gilbertie et al	X	X	>10,000 cells/μL	X	X	X	X	X	√	Supprative or fibrinous inflammation at PME
Isgren et al	≥1 of the following[a]	X	≥10 x 10^9 cells/L	>80%	>30 g/L	√	Intracellular bacteria	√	X	
Milner et al	X	X	≥5 x 10^9 cells/L	>80%	>30 g/L	√	X	√	X	
Rubio Martinez et al	≥3 of the following	X	>30,000 cells/μL	>90%	>4 g/dL	√	Organisms present, degenerative changes to PMN	X	X	
Wereszka et al	X	X	>30,000 cells/μL	>90%	>4 g/dL	√	X	X	X	Clinical parameters suggestive of synovial sepsis (lameness, heat, effusion of DFTS, surgical findings)
Wright et al	X	√	√	X	√	X	X	√	X	

Abbreviations: √, included inclusion criteria; DFTS, digital flexor tendon sheath; PME, post-mortem examination; PMN, polymorphonuclear leukocytes; SF, synovial fluid; X, not specified.

[a]Needed all SF parameters to be elevated to count as 1 of the criteria.

TABLE 3 Key findings of studies that reported risk factors affecting outcome after synovial sepsis in the horse

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Horse factors	Nail penetration	Findley et al (2014)	Group 2 breeds (Thoroughbred/Thoroughbred crosses, Warmbloods/Warmblood crosses and Arabs) were less likely to return to the pre-injury level of activity than Group 1 breeds (cobs, ponies, draught breeds and draught breed crosses) (OR 32.1, 95% CI 2.2-135.4, $P = .001$)
		Rubio Martinez et al (2012)	Mares were more likely to survive than geldings (OR 9.814, 95% CI, 1.798-53.559, $P = .03$), and intact males were more likely to survive than geldings (OR 5.33, 95% CI, 0.619- 45.9, $P = .03$).
		Wright et al (2003)	In horses that survived, non-Thoroughbred horses had significant associations with reduced post-operative performance compared with Thoroughbreds and Thoroughbred-X (OR 6.256 95% CI 1.248-31.371 $P = .026$)
Synovial structure (s)		Rubio Martinez et al (2012)	The probability to return to performance at a level equal to or higher than before the injury was higher for horses in which the hindlimb was involved, compared with those in which the forelimb was involved (OR 16.44, 95% CI 1.71-110.23, $P = .028$).
		Rubio Martinez et al (2012)	Horses with a single synovial structure involved were more likely to survive long-term than horses with multiple synovial structures (including synovial tendon sheaths, bursae and joints) involved (OR 6.205, 95% CI 1.168-32.952, $P = .032$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses with sepsis of an adjacent joint were less likely to survive at least 1 year after surgery, compared with horses without evidence of sepsis of an adjacent joint (OR 0.131, 95% CI 0.015-0.0947, $P < .044$).
		Wright et al (2003)	In horses that survived, a combination of synovial structure involvement had significant associations with reduced post-operative performance compared to single synovial involvement (joint, tendon sheath, bursae) (OR 7.250 95% CI 1.244-42.259, $P = .028$).
Injury	Nail penetration	Findley et al (2014)	Direct penetration of the central sulcus of the frog was associated with euthanasia during hospitalisation (OR 10, 95% CI 1.9-51.8, $P = .002$).
		Milner et al (2014)	Presence of a wound on admission was associated with increased likelihood of survival (OR 4.75, 95% CI 1.21-18.65, $P = .02$).
Duration of clinical signs prior to referral	Nail penetration	Findley et al (2014)	Increasing number of days to presentation was significantly associated with failure to return to pre-injury level of athletic function (OR 1.1, 95% CI 1.1-1.6, $P < .0001$).
	Nail penetration	Findley et al (2014)	Increasing number of days from injury to presentation was associated with euthanasia during hospitalisation (OR 1.2, 95% CI 1.0-1.3, $P = .006$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses in which duration of clinical signs was <1 day were significantly more likely to survive at least 1 year after surgery, compared with horses in which duration of clinical signs was >10 days (OR 15.6, 95% CI 1.24-500, $P < .027$).
Treatment prior to referral	Calcaneal bursae	Isgren et al (2020)	The administration of systemic antimicrobials prior to referral was associated with reduced mortality (HR 0.25, 95% CI 0.11-0.60, $P = .002$).
Synovial fluid analysis pre-operatively		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with coagulase positive Staphylococcus spp. (OR 7.66, 5.46-10.74, $P < .0001$), β-haemolytic *Streptococcus* spp. (OR 5.18, 3.56-7.55, $P < .0001$), *Enterococcus* spp. (OR 18.38, 11.45-29.52, $P = .002$), *Enterobacteriaceae* (OR 31.37, 22.28-44.17, $P < .0001$), *Pseudomonas aeruginosa* (OR 9.31, 5.30-16.34, $P = .0004$) or other Gram-negative species (OR 3.51, 2.07-5.94, $P = .001$).
		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with infections by Gram-negative organisms (OR 5.03, 3.77-6.72, $P < .0001$)
		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with multi-drug resistance (MDR) (OR 16.11, 12.09-21.45, $P < .0001$)
		Gilbertie et al (2018)	Increased likelihood of euthanasia for MDR Gram-positive organisms (OR 1.85, 1.21-2.81, $P < .005$) and Gram-negative organisms (OR 119.24, 70.57-201.46, $P < .0001$)
		Milner et al (2014)	Higher synovial fluid TP levels measured on admission were associated with a reduced likelihood of survival (OR 0.88, 95% CI 0.83-0.94, $P < .001$).

(Continues)

TABLE 3 (Continued)

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Presence of pannus		Milner et al (2014)	Horses with evidence of moderate/severe synovial inflammation identified during endoscopic examination were around four times less likely to survive to discharge than horses with no synovial inflammation (OR 0.28, 95% CI 0.12-0.67, $P = .004$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Presence of severe pannus was significantly associated with a decreased likelihood of returning to a previous or higher level of performance (OR 0.067, 95% CI 0.010-0.455, $P < .006$).
		Wright et al (2003)	For horses that returned to performance, the presence of pannus had significant associations with reduced post-operative performance and nonsurvival (OR 2.839, 95% CI 1.013-7,995, $P = .047$).
		Wright et al (2003)	Presence of marked pannus was significantly associated with nonsurvival compared with moderate/minor or no pannus (OR 5.487, 95% CI 1.081-27.854, $P = .040$).
Tendon injury	Calcaneal bursae	Isgren et al (2020)	Moderate/severe tendon involvement (≥30% cross sectional area) was associated with increased mortality (HR 7.95, 95% CI 3.33-19.0, $P < .001$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses with partial or complete tendon rupture were significantly less likely to survive at least 1 year after surgery, compared with horses without evidence of tendon rupture (OR 0.064, 95% CI 0.003-0.554, $P < .026$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	The presence of tendon injuries (fraying or tearing of the tendon seen during surgery or tendonitis diagnosed ultrasonographically) (OR 0.094, 95% CI 0.013-0.674, $P <.019$) were significantly associated with a decreased likelihood of returning to a previous or higher level of performance.
Bone pathology	Nail penetration	Findley et al (2014)	Concurrent injury to the pedal bone was associated with euthanasia during hospitalisation (OR 32.1, 95% CI 2.6-101.9, $P = .005$).
		Wright et al (2003)	Presence of osteochondral pathology was significantly associated with nonsurvival (OR 6.38, 95% CI 1.31-31.03, $P = .022$).
		Wright et al (2003)	Presence of osteomyelitis was significantly associated with nonsurvival (OR 6.259, 95% CI 1.651-23.654, $P = .007$).
Number of surgeries	Nail penetration	Findley et al (2014)	More than one surgery was significantly associated with failure to return to pre-injury level of athletic function (OR 5.6, 95% CI 1.0-32.7, $P = .03$).
		Milner et al (2014)	Horses undergoing greater than one endoscopic procedure were around 5 times less likely to survive to hospital discharge (OR 0.19, 95% CI 0.05-0.70, $P = .005$).
Surgical factors	Nail penetration	Findley et al (2014)	The hospital at which the horse was treated was associated with failure to return to the pre-injury level of athletic function (OR 2.9, 95% CI 0.6-14.6, $P < .0001$) (OR 0.5, 95% CI 0.003-0.8, $P < .0001$) (OR 1.4, 95% CI 0.2-9.9, $P < .0001$).
	Nail penetration	Findley et al (2014)	The hospital at which the horse was treated was associated with euthanasia during hospitalisation (OR 0.1, 95% CI 0.3-0.9, $P = .006$) (OR 0.2, 95% CI 0.02-0.8, $P = .006$) (OR 0.01, 95% CI 0.007-0.4, $P = .006$).
		Milner et al (2014)	Anaesthetic induction during normal working hours was associated with increased likelihood of survival (OR 0.36, 95% CI 0.15-0.88 $P = .02$). Horses undergoing anaesthetic induction outside of normal working hours were around three times less likely to survive to hospital discharge.
Lavage technique		Rubio Martinez et al (2012)	Horses that were not treated with intrasynovial continuous lavage with isotonic fluids were more likely to return to the same or higher level compared with those in which ISCL with isotonic fluids was used (OR, 43.99, 95% CI, 1.929 to >999.999; $P = .018$).

(Continues)

TABLE 3 (Continued)

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Regional antimicrobials		Wright et al (2003)	For horses that returned to performance, the use of regional IV antimicrobials had significant associations with reduced post-operative performance and nonsurvival (OR 3.192, 95% CI 1.085-9.394, $P = .035$).
		Wright et al (2003)	In horses that survived, use of regional IV antimicrobials had significant associations with reduced post-operative performance compared with not using regional IV antimicrobials (OR 4.256 95% CI 1.056-17.153, $P = .042$).
Systemic antimicrobials		Crosby et al (2019)	For return to function when considering each individual synovial structure, treatment with doxycycline was negatively associated with return to function (OR 0.39, 95% CI 0.19-0.8, $P = .031$).
		Crosby et al (2019)	Increasing number of days of treatment with systemic antimicrobials was associated with increased likelihood of survival for each horse (OR 1.15, 95% CI 1.04-1.27, $P = .025$) and when considering each individual synovial structure (OR 1.11, 95% CI 1.04 − 1.17, $P = .004$).
		Rubio Martinez et al (2012)	Higher long-term survival rates for horses that received systemic antimicrobials prior to admission compared with those that did not receive systemic antimicrobials (OR,11.89, 95% CI 2.017-70.181, $P = .006$).
		Wright et al (2003)	For horses that returned to performance, the duration of systemic antimicrobials >7 days had significant associations with reduced post-operative performance and nonsurvival (OR 13.960, 95% CI 1.786-109.133, $P = .012$).
		Wright et al (2003)	For horses that returned to performance, the use of systemic antimicrobials >12 days had significant associations with reduced post-operative performance and nonsurvival (OR 15.429, 95% CI 1.891-125.862, $P = .011$).
Synovial fluid analysis post-operatively		Milner et al (2014)	Synovial fluid TP value measured post-operatively was significantly associated with survival (likelihood of survival decreasing as TP values increased) (OR 0.94, 95% CI 0.90-0.98, $P = .013$).

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; DFTS, digital flexor tendon sheath; HR, hazards ratio; ISCL, intrasynovial continuous lavage; IV, intravenous; MDR, multidrug resistance; OR, odds ratio; TP, total protein.

[a]If structure or nature of injury not specified it relates to general synovial structures (which can include joints tendon sheaths and bursae) caused by a range of inciting causes.

bacteria colonisation.[14,49] One study separated horses with "fresh intrasynovial lacerations with minimal contamination" from horses with established synovial sepsis,[14] whereas confirmation of synovial involvement was a criterion of inclusion for others.[1,2,11,49]

The treatment techniques involved lavage, systemic and regional antimicrobials in six of eight studies.[1,2,9-11,49] In one study, a specific surgical technique of regional limb perfusion was described.[14] Treatment techniques were not specified in one paper.[15] The outcome measured for all eight studies was survival to hospital discharge with or without including return to athletic function. The timeframe of follow-up differed between the studies; two studies looked at survival without residual lameness,[2,15] whereas six studies had a range of follow-up times between three months and 16 years post-operatively. Three studies used an objective measurement of outcome using race records either solely or in combination with telephone questionnaires[10,11,49] with three other studies using only telephone questionnaires to owners, trainers or referring veterinarians for follow-up.[1,9,14]

Table 3 demonstrates the 15 risk factors that were found to be statistically significant evidence of association including: horse factors, synovial structure, type of injury, duration of clinical signs prior to referral, treatment prior to referral, synovial fluid analysis pre-operatively, presence of pannus, tendon injury, bone pathology, number of surgeries, surgical factors, lavage technique, regional antimicrobials, systemic antimicrobials, synovial fluid analysis post-operatively. Table 4 highlights the number of studies within each category of risk factor divided into pre-operative (n = 6), intraoperative (n = 6) and post-operative factors (n = 3).

4 | DISCUSSION

This scoping review has identified the pertinent and current literature available on treatment for synovial sepsis and found a varied group of 61 studies from fourteen countries. From these sixty-one studies, eight have been identified that report significant risk factors and outcome. Within this body of literature, key issues that have been identified include the lack of consistency in inclusion criteria and follow-up duration and measurement of outcome between studies, and the small number of studies that identify significant risk factors.

TABLE 4 Summary of studies reporting significant risk factors affecting treatment outcome after synovial sepsis

	Risk factor type	Number of studies
Pre-operative	Horse factors	2
	Cause of injury	2
	Synovial structure involved	3
	Synovial fluid analysis	2
	Treatment prior to referral	1
	Duration of clinical signs prior to referral	2
Intraoperative	Bone pathology	2
	Tendon pathology	2
	Presence of pannus	3
	Surgical factors	2
	Lavage	1
	Number of surgeries	2
Post-operative	Systemic antimicrobials	3
	Regional antimicrobials	1
	Post-operative synovial fluid analysis	1

4.1 | Summary of evidence – research conduct

4.1.1 | Definitions

"To advance knowledge of a clinical entity, we must begin with a definition".[50] Refining inclusion criteria for horses with synovial sepsis is a difficult undertaking as it is a broad term used to describe a dynamic pathological process of a vast range of clinical presentations. There are currently no evidence-based recommendations for inclusion criteria or diagnosis for cases of synovial sepsis. Of the eight studies identified within this scoping review that report risk factors affecting outcome after synovial sepsis, there were marked differences in diagnostic criteria for synovial fluid "cut-off" parameters and varied differentiation and separation of contaminated or infected synovial structures. By using different definitions, this resulted in different subsets of horses being included and investigated under an umbrella term of synovial sepsis, making comparisons of results between studies impossible. Previous scoping reviews have identified this issue within different bodies of literature and acknowledge that variability identified in inclusion criteria of study subjects can restrict the ability to conduct systematic reviews.[51] Establishing agreement with inclusion criteria is a common issue within research settings. In human literature, consensus methods are often used to provide guidelines regarding key features of pathology and treatment, as well as creating diagnostic criteria for specific diseases.[52,53] Consensus methods include techniques such as nominal group processes, consensus development panels, and Delphi techniques, and are based on evidence based medicine. If this is not available then recommendations are based on knowledge and expertise of specialists through a set protocol of discussion.[53,54] Their findings should be frequently reviewed in order to adapt with changing evidence and practice.[52] There are several consensus statements within veterinary scientific writing, which provide guidelines and recommendations to other practitioners and researchers for specific diseases.[55] There is currently no consensus statement for synovial sepsis and this could significantly improve future research if clarity and agreement over inclusion criteria could be implemented.

4.1.2 | Measurement of outcome

There were key differences identified in the measurement of outcome variables. The main measurements of outcome after synovial sepsis were survival to hospital discharge and/or return to athletic function (Table S1). Of the studies that looked at return to athletic function, this was defined differently. Some studies looked at survival without residual lameness,[2,15] whereas others tried to quantify the level at which the horse was working either subjectively with telephone questionnaires[1,9,14] or objectively in combination with online race records.[10,11,49] Cook et al, has proposed a set of definitions reporting outcomes for clinical orthopaedic trials and suggests using the terms return to "full function", "acceptable function" and "unacceptable function".[56] This framework, if implemented, could provide guidance for authors as well as consistency between studies. There were also differences in the time frame of "long-term" follow-up and the method of follow-up between studies. There was a large range in the follow-up duration between studies from 3 months to 16 years post-operatively. Defining and stating the duration of follow-up more transparently and implementation of standardised time frames would make interpretation of outcome measurements clearer. Again, the lack of consistency means consolidation of the evidence and interpretation of studies investigating return to athletic function remains challenging and further evidence synthesis, including a systematic review, is not possible.

4.1.3 | Study design and conduct

Study design features that were identified as limiting the quality of evidence included the small number of studies that accounted for confounding variables, the lack of treatment details described within the materials and methods, and the small sample sizes. Within the 61 studies, 18 cross-sectional studies were identified that investigated outcomes following synovial sepsis, which did not account for confounding factors within their statistical analysis (Table S2). Only eight studies were identified to take into consideration confounding factors and used multivariable analysis. Multivariable analysis is an essential statistical tool to enable complex relationships to be established between several variables and should be used in studies where study design is unable to account for confounding bias.[57,58]

In addition, adequate details of treatment techniques were often lacking. Of the eight studies identifying significant factors affecting outcome, six of eight described some form of treatment technique

involving lavage, systemic and regional antimicrobials with one study not specifying any treatment techniques used at all. Significant details of surgical techniques including wound resection and closure, synovial resection, lavage fluid and volume or drainage could be important variables affecting treatment outcome. This can be accounted for if the studied population all receive the same treatment, and this is clearly stated during the study design process; however, if these are not controlled nor described then further details of treatment techniques should be included within the results to allow comparisons and improve the external validity of the research. This is a common finding within the studies identified and may be due to the retrospective nature of the study design, with data being collected from clinical case records. This could be improved in the future by standardised reporting and inclusion of clear descriptions of surgical techniques either within the study design or results. In addition, the use of prospective study designs investigating these factors could be of benefit to assessing confounding variables.

Sample size is a common limitation of veterinary and human research.[59] This scoping review identified that within the 61 studies initially identified, 80% of the studies had less than 60 subject participants. Of the eight studies that identified specific risk factors, one contained less than 60 subjects[9] and seven included more than 61 subjects. The power of a study increases with sample size.[59,60] This is applicable to investigating outcomes after synovial sepsis when differences between outcomes are small. Death after treatment of synovial sepsis is relatively infrequent and the differences between horses reaching a better or worse level of athletic function are likely to be small and multifactorial. Larger sample sizes can improve the ability to detect small differences or investigate multiple variables and can facilitate more robust statistical modelling, thereby improving the quality of the data.[61,62] Most studies investigated data from a single hospital (68.9%), with only seven studies investigating data from three or more hospitals, which likely contributed to the small number of study participants. Multicentre and multinational studies provide both access to a larger sample size increasing the ability to detect small differences as well as providing greater variety of the population studied, enabling the results to be applicable to the general population.[63]

4.2 | Summary of evidence – key findings and factors identified

The findings from the small number of studies with similar risk factors were categorised into three groups, and this identified that there were six pre-operative, six intraoperative and three post-operative risk factors. Within these categories, the most commonly represented risk factors were the number of synovial structures involved,[9,10,14] the presence of pannus,[2,9,10] presence of tendon and bone pathology[1,9,10,49] and the use of systemic antimicrobials.[10,11,14]

Although no risk assessment was performed, this scoping review identified themes within these studies. Interestingly, from those studies that investigated all synovial structures (including tendon sheaths, bursae and joints), no specific synovial structure was reported to have a worse or better prognosis. However, three studies found that horses with injuries involving multiple synovial structures had a reduced likelihood of survival.[9,10,14] In addition, five studies identified that more severe injuries with concurrent tendon injury,[9,49] bone pathology[1,10] or presence of moderate to severe pannus[2,9,10] were significant negative prognostic indicators for both survival and return to work. However, establishing detailed criteria and grades for different tendon, bone and synovial pathology is necessary to further determine the nuances of these associations.

The use of systemic antimicrobials was found by three studies to affect survival and return to work.[10,11,14] Rubio-Martinez et al found horses that received systemic antimicrobials prior to admission had higher survival rates compared to those that did not. This finding has not been previously reported and suggests that early intervention can improve outcomes. Crosby et al found that the use of a specific antimicrobial, doxycycline, was associated with a negative outcome. The authors suggested that typically doxycycline was used for refractory cases in their population. This may have skewed its use towards cases that had not responded to initial broad-spectrum antimicrobials. The presence of a wound communicating with the synovial structure was found to be a factor associated with better survival.[2] One hypothesis from that study was that this was due to earlier identification of wounds by clients compared with more insidious causes of synovial sepsis, which may allow earlier implementation of treatment.[2] All eight of the studies in Table 3 investigated how timing of the injury prior to referral affected outcome. Surprisingly, only two studies found a significant association with duration of injury prior to referral with a poorer prognosis for survival and return to work.[1,9] It is anecdotally believed that there is a "golden" window in which treatment for synovial sepsis carries a greater chance of success; however, there is a lack of robust evidence within this body of literature to support this impression. Early recognition of wounds, increased awareness of synovial structures and implementation of treatment is undeniably desirable and further research into owners' and veterinarians' initial triage of potential synovial sepsis cases is important to further quantify these associations.

This scoping review highlights that only a small number of studies have found associations with similar risk factors, which would make these associations difficult to analyse with a systematic review; however, themes that have been identified and could warrant future investigation include how early recognition influences the early implementation of antimicrobial treatment, bone and tendon involvement and intrasynovial pannus formation.

4.3 | Limitations of the scoping review

There are several inherent limitations to the scoping review process. A scoping review does not provide analytical critique of the literature compared with a systematic review nor does it specifically answer a research question.[21] It can provide an overview without specific details or assessment of risk within the published work and identify bodies of evidence for more detailed analysis through a systematic review.[21] Broad search terms and inclusion criteria were

used to capture as many of the appropriate studies as possible using the key veterinary research databases including Medline, CAB abstracts and Scopus,[29] which were outlined in the a priori protocol; however, this search strategy did not identify some studies, which would have met the inclusion criteria, and had been identified by a hand search of the references of the included studies. An additional search engine, Embase, was included after the initial searches, which allowed further studies to be captured likely due to differences in indexing and inclusion of additional journals.[29] Quality control check points for search strategies should be implemented in scoping reviews, or independent assessment to ensure an appropriate breadth and representative literature is captured.

Conference proceedings and full texts not in English language where no translation was available were excluded. Conference proceedings offer an important source of new data often prior or exclusive to publication elsewhere, with some studies suggesting less than 10% of conference proceedings being subsequently published.[64] In addition, there may be a selection bias for conference proceedings with positive results to be subsequently published and, therefore, the results of conference proceedings may offer a true representation of both positive and negative results.[65] An extensive search strategy was performed to gain access to the full papers; however, 15 studies were not available, 12 of which were abstracts from conference proceedings. It could benefit future work if conference proceedings were more widely accessible with effective dissemination.

Several steps were taken to reduce bias and subjectivity within the methodology. An a priori protocol was developed and inclusion and exclusion criteria developed after collaborative discussion between authors. The search terms used were developed by the authors with consultation from an experienced librarian to help with specific database nuances. Systematic assessment of the studies was performed independently by two authors, with any ambiguous titles or abstracts being taken through to the next round of assessment; however, the charting process was performed by one author and verified by all others, which could have led to selection bias. It has been suggested to use two authors to independently chart all texts and to discuss any discrepancies that could reduce this selection bias in the future.[22,66]

Scoping reviews can act as an evidence synthesis tool, as well as providing an evidence-based precursor to performing a systematic review. At this stage, although no further critical analysis of the relevant risk factors was presented, the limited number and poor compatibility between studies would mean a systematic review would not be possible as an additional evidence synthesis tool. This is a common conclusion of scoping reviews; Tricco et al found only 12% of scoping reviews included a recommendation of a systematic review in their conclusions.[22]

5 | CONCLUSION AND RECOMMENDATIONS

This scoping review has extracted and categorised the current evidence relevant to treatment outcomes after synovial sepsis to aid clinicians, and to inform future research.

Key future research recommendations include the following:

- The development of standardised inclusion criteria for cases of synovial sepsis and more comparable measurements of outcome are essential for more detailed evidence synthesis of this body of literature to occur.
- Use of methodologies to reduce bias including multicentre and multinational studies, prospective study design and robust statistical modelling.
- Standardised reporting of treatment techniques within study design descriptions.

Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology and the use of systemic antimicrobials. Future areas of research are important to establish criteria and grades for different tendon, bone and synovial pathology and to assess the effect of early recognition of synovial sepsis and implementation of treatment on desirable outcomes.

CONFLICT OF INTERESTS

No competing interests have been declared.

AUTHOR CONTRIBUTIONS

All authors contributed to study design and methodology. T. de Souza and S. Freeman carried out the database searches and exclusion, with consultation of other authors if required. Data extraction and interpretation was performed by all authors. All authors contributed to manuscript preparation and critical review.

ETHICAL ANIMAL RESEARCH

The study was reviewed and approved by the School of Veterinary Medicine and Science Ethics Committee, University of Nottingham.

INFORMED CONSENT

Not applicable.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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